        - If IND-enabled, should put drug in separate category. Specify that we are interested in repurposed drugs, drugs that are IND enabled.
        -
        - Even for an approved agent, may need to enter into phase 1 pilot phase. We cannot assume that the current dose for drug is the right dose for these patient populations.
    - Suggestion to score the criteria
        - May need to break down criteria further down into sub criteria.
        - May be difficult to score / scoring system necessary if only a few drugs?
- Suggestion for RFI, and sponsors can submit their ideas in a way that facilitates this WG's review – category, mechanism of action, etc. should be aligned and clear.
    - Given timelines, suggestion for RFI is to focus on "second wave" drug that are close to clinic ready or in Phase I. Possible some late preclinical.

Chatbox

From (b) (6) [redacted] to Everyone: 05:34 PM

Thank you for the new materials. Helpful.

From (b) (6) [redacted] to Everyone: 05:34 PM

Very good. Glad they are.

From (b) (6) [redacted] to Everyone: 05:38 PM

(b) (4) [redacted] For example, (b) (4) [redacted]

From (b) (6) [redacted] to Everyone: 05:39 PM

There was some discussion that (b) (4) [redacted]

From (b) (6) [redacted] to Everyone: 05:45 PM

Sure, but these are hardly (b) (4) [redacted].

(b) (4) [redacted] Example (b) (4) [redacted]

Yes, excellent approach

From (b) (6) [redacted] to Everyone: 05:50 PM

(b) (4) [redacted]

From (b) (6) [redacted] to Everyone: 05:54 PM

Tuesday, April 14th, 2020

Tim would you like to chime in on this third category?

From (b) (6) **to Everyone: 05:55 PM**

(b) (4)

From (b) (6) **to Everyone: 06:18 PM**

(b) (4)

From (b) (6) **Everyone: 06:28 PM**

The (b) (4) studies are of course in progress.

High-Level Meeting Summary

The Master Protocol Subgroup of the TX-Clinical Working Group (WG) explored major considerations shaping the design of a master protocol for candidate COVID-19 therapeutics.

The Subgroup's immediate priority is to designate the patient populations that the master protocol will address; this information has been requested by the Clinical Capacity WG, which will inventory clinical trial networks that can enroll patients under the protocol. Members broadly agreed on the need for a master protocol that addresses patient populations across the spectrum of illness, with a particular focus on hospitalized and ambulatory patients.

The Subgroup must next determine the number and nature of master protocols needed to advance this goal and must assess whether characteristics deemed essential are available in existing master protocols or require a new protocol design. Members agreed they need to examine these questions further in a subsequent meeting. A summary of the discussion follows.

Lessons from a Parallel Effort

The Subgroup discussed a (b)(4) [redacted] Drs (b)(4), (b)(6) [redacted] and (b)(4), (b)(6) [redacted] described an effort by (b)(4) [redacted] [redacted]

ACTIV will also encounter:

- (b)(4) [redacted]
-
-

Defining the Patient Population

The Subgroup agreed that the ACTIV master protocols must be nimble enough to enroll three heterogeneous patient populations: (1) ambulatory outpatients with moderate symptoms, (2) hospitalized inpatients, and (3) ICU patients. This breadth will enable trials to transcend often-artificial distinctions in disease progression (e.g., ambulatory patients may use oxygen at home, and some will progress to hospitalization). It will also sustain the master protocol's relevance as trial data continuously reshapes efforts. The Subgroup agreed, however, that the master protocol will not encompass trials of prophylactic interventions for high-risk groups.

Simultaneous vs. Successive Study

Hospital-based enrollment could allow simultaneous recruitment and study of multiple patient populations, whereas a "wave" approach (the Agent Prioritization subgroup has adopted such an approach for evaluating candidates) would support successive examinations of populations. If the wave approach is pursued, the Subgroup agreed that the first wave should prioritize hospitalized non-ICU and ambulatory patients. The Subgroup acknowledged (b) (4) [redacted] (e.g., (b) (4) [redacted] However, participants also noted (b) (4) [redacted]

Selection of Endpoints

The Subgroup agreed that while precise endpoints will differ by patient population, they should generally be based on simple established measures in order to streamline efforts and promote comparability across trials. The WG designated the 8-point NIH clinical scale as a prime candidate.

Developing a New Master Protocol or Leveraging an Existing One

The Subgroup has the expertise needed to establish an entirely new protocol, but also has expansive knowledge of existing protocols that could be feasibly adjusted to support ACTIV's goals. The Subgroup agreed that *speed* will be the decisive factor in choosing between these two approaches.

Existing Master Protocols

The Subgroup has collated specific U.S.-based and international model protocols (such as ACTT, PRINCIPLE, REMAP-CAP, and ORCHID) with a variety of characteristics, ranging from the well-established (e.g., concurrent shared control arms) to the more complex (e.g., response-adaptive randomization) . The Subgroup must review these protocols to identify any that could be used, in their entirety or in component form, by ACTIV.

The Subgroup also discussed the possibility of *joining* an existing protocol. Participants noted that some protocols under discussion are designed to accept new arms (for example, ACTG has an outpatient population study ready to open on or around May 1). However, some participants cautioned that this path poses operational challenges that seem incompatible with the urgency of ACTIV.

Next Steps

The Subgroup decided to reconvene quickly in order to translate the considerations identified during this meeting into parameters for a master protocol, to assess whether those parameters are available in existing master protocols or require design of a new one, and to begin writing the ACTIV master protocols (whether adapted or new).

Appendix A: Participants List

SUBGROUP MEMBERS

Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Joan Butterton, MD, *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*

Sylva Collins, PhD, *Director, Office of Biostatistics, FDA*

Judy Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Mark Eisner, MD, MPH, *Senior Vice President and Global Head of Immunology, Infectious Disease and Ophthalmology, Genentech*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

Lisa LaVange, PhD, *Professor and Associate Chair, Department of Biostatistics, UNC Chapel Hill (Master Protocol SG chair)*

Elliott Levy, MD, *Senior VP Global Development, Amgen; TransCelerate Board Member*

Sandeep Menon, PhD, *Senior VP and Head of Early Clinical Development, Pfizer*

Amanda Peppercorn, MD, *Senior Medical Director, Infectious Disease, GlaxoSmithKline (GSK)*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Mike Vincent, MD, PhD, *Senior VP, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

INVITED PARTICIPANTS

Yuan-Li Shen, PhD, *Biostatistician, Acting Deputy Director, Division of Biometrics V, FDA*

Dionne Price, PhD, *Office of Biostatistics of the Center for Drug Evaluation and Research, FDA*

Daniel Rubin, PhD, *Statistician, Center for Drug Evaluation and Research, FDA*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Elizabeth Kim, MPP, *Senior Consultant, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From (b) (6) [redacted] to Everyone: 01:57 PM

I have a question about how we decide (b) (5) [redacted]

From (b) (6) [redacted] to Everyone: 02:00 PM

hey (b) (6) [redacted] the key word (b) (5) [redacted]

From (b) (6) [redacted] to Everyone: 02:04 PM

I understand that the intent is not necessarily to have a (b) (5) [redacted] That has a number of disadvantages, especially in infectious diseases.

From (b) (6) [redacted] to Everyone: 02:06 PM

No argument here, but I do like (b) (5) [redacted]

From elliottl to Everyone: 02:14 PM

worth clarifying FDA requirements…certain types of protocols may be incapable of satisfying them

From Stacey Adam to Everyone: 02:15 PM

Thanks Elliott, would you like to do that on the call or offline between our calls for reference?

From elliottl to Everyone: 02:16 PM

can be done offline

From Stacey Adam to Everyone: 02:16 PM

Okay, thanks

From (b) (6) [redacted] Everyone: 02:27 PM

(b) (5) [redacted] If so, what is the proportion?

From Stacey Adam to Everyone: 02:28 PM

Not sure Mark, but we can get that answer offline if not here

From sam bozzette to Everyone: 02:36 PM

im fiune with meeting at 11 EDT tomorrow

fine

and think it good idea

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group

Working Group Meeting 2, Key Takeaways

Thursday, April 16th, 2020

Action Items

Action Items		
	Information	**POC**
1	WG co-chairs and subgroup chair to draft hybrid Master Protocol action items list and timelines and share with WG	**Lisa LaVange, Sarah Read, Eric Hughes, Stacey Adam**

Key Takeaways

- ACTIV should take a **broad approach to thinking about patient population.** Include outpatient and in-patient populations, do **not to differentiate between ICU and non-ICU**. Populations can be tailored to interventions down the road. **Prophylaxis/prevention interventions review will be postponed for now.**
- Agreement on patient population categories: **Prophylaxis, Outpatient/Ambulatory ill, Hospitalized/moderately ill (non-ICU), critically ill/ventilated (ICU).** Priority focus will be on the inpatient population without differentiating between ICU or not. Outpatient would be our second priority population, and then beyond that would be prophylaxis/prevention of disease.
- WG is moving forward in considering a **hybrid approach** to a Master Protocol, and WG leads will draft an action item list to compare timelines of building a Master Protocol *de novo* and doing an ACTT 3 in parallel. If ACTIV develops own protocol, it will need to be differentiated. If we can build something that gives us fast answers to treatments now, then can be expanded to prophylaxis, and can be ready for next summer, that could be our differentiation.

Patient Populations

- We want to think broadly about the patient population and not be too narrow. Treatments will be driven by patient subgroups.
- Divide patients into outpatient and in-patient populations, and then within inpatient populations, not to divide between ICU and non-ICU. Interventions can be tailored down the road. Prophylaxis/prevention interventions off the table for now.
- There are some compounds that should only be used in end-stage approach. Some sort of delineation between end stage patients who are in patient and those who are not will still be important.
- Considerations:
    - Platform – treatments should come and go as they are ready
    - Precision health aspect – acknowledgement that there will be patient subtypes that can't receive all of the drugs.
    - Group agreement on the ability to allow standard of care to evolve with evidence.
        - Having a common standard of care may be less important when thinking about statistics design.

    - Different SOCs may align with patient types.

- FDA perspective:
  - (b) (5) [redacted]
  -

- Clinical Trial Capacity and Therapeutics Clinical WGs alignment on Patient populations
  - Both groups have identified similar patient categories but are using different terminology.
  - Group consensus on the following patient populations:
    - Healthy non-infected individuals, with the aim of intervention/prevention of disease (also prophylaxis/prevention)
    - Infected individuals observed at home, with aim of preventing progression/more severe (outpatient/ambulatory ill)
    - Individual that require care for hypoxemia (hospitalized/moderately ill, non-ICU)
    - Treatment to prevent mortal/morbid complications (critically ill/ventilated, ICU)
- Agreement on the categories: Prophylaxis, Outpatient/Ambulatory ill, Hospitalized/moderately ill (non-ICU), critically ill/ventilated (ICU)
  - Sometimes there may be an overlap between two categories – ex) some that are "critically ill" may have been "moderate" because they didn't have access to ventilators.
- Our goal is to test as many compounds as efficiently as we can. We want to know which populations to test first to get to those results. In this effort, we will focus on hospitalized/moderately ill, non-ICU and critically ill/ventilated, ICU. Outpatient/ambulatory ill would be our second priority population, and then beyond that would be prophylaxis/prevention of disease.
- What are the endpoints for inpatient and outpatient setting to quickly evaluate activity of the agents? This is an area of a lot of variability across existing trials.
  - Need to rely more on clinical endpoints versus virological; the latter are not yet reliable.

Master Protocol Options Discussion

- Goal is to find the best approach, most efficient way, to study multiple compounds and get data as soon as possible.
- Commentary from the group on different Master Protocols:
  - (b) (5) [redacted]
    - (b) (5) [redacted]

        - (b) (5)
    - (b) (5)
        - (b) (5)
    - (b) (5).
        - (b) (5)
        -
    - (b) (5)
- Discussion on potential for ACTIV build own Master Protocol:
    - If we build our own, need to differentiate ourselves. If we can build something that gives us fast answers to treatments now, then can be expanded to prophylaxis, and can be ready for next summer, that would be our differentiation.
    - In the fall and winter, there is a rollout of mAbs and other clinically ready small molecules. We need the capacity to study protocols and evaluate which is most effective.
    - Concern about cannibalization. Some sites are overwhelmed and not interested in taking new studies. They would need incentivization.
- Discussion on potential for ACTIV to merge/build on existing:
    - We do not know what else trials will do, what else they will add, different populations, etc. If these other studies have plans to expand, we could merge with them.
    - There are efficiencies to gain from selecting a few Master Protocols and using what's out there, rather than starting from scratch.
- Promotional aspects
    - The hope is that others will merge into our effort. If Francis Collins says that this is an NIH PPP, people will think instead of doing their smaller trial, NIH PPP trial better because it is broader and more expansive.

  - We want a national testing strategy, a unified approach, global reach, and having a unified platform may be better for messaging.
  - If this is seen as gold standard, people may be eager to join.
  - We could take from existing protocols the endpoints of the populations.
- Hybrid approach suggestion:
  - Suggestion to have both a master protocol that ACTIV develops and do an ACTT 3, running in parallel, but with harmonized endpoints and structures.
  - Observation: we have gotten faster with every MP, CTC WG has members of NCI clinical trial networks who know how to build and add on to existing protocols. The last modification/revamp of Lung-MAP was fast.
  - Concern from the group about duplicating work.

Next Steps

- Draft action item list for the build and timelines for developing Master Protocol de novo vs. ACTT 3 approach.
- Then discuss optimal networks, potential challenges with central IRB, etc.

Additional Considerations

- All patients will be under one umbrella, one master protocol.
- We're thinking big; this should be the national platform for things. We're thinking for the future.
- Unification and messaging: we want a unified front, unified platform, but we don't want to pirate/take away from trials that are out there.
- Possibility of writing what is essentially a master screening protocol that could feed into the other master protocols? Then the screening platform becomes the unification, and we can still be speedy by repurposing the other trials.
- Using the language "repurpose" is important. We're using what's out there as a starting place
- WG could create a discussion document for the ACTT leadership as basis for their third stage trial. We'd learn very quickly if repurposing under existing protocol is viable.

High-Level Meeting Summary

The ~~Therapeutics-Clinical~~Clinical Trial Capacity Working Group (WG), co-chaired by Drs. Elizabeth Desrosiers and Michael Kurilla, convened to discuss and strategize on approaches to fulfill its charge to maximize the capacity and utilization of clinical trials to identify effective therapeutics and vaccines for COVID-19. To start, the WG will develop an inventory of the clinical trial networks (CTNs) and sites that have the capacity to conduct trials of the therapeutics prioritized by the Clinical Therapeutics WG and to report outcomes by June or July.

WG members highlighted the importance of moving sites that are fit for purpose and can quickly launch a new trial into clinical trials as soon as possible, especially trials of repurposed compounds. They agreed that the traditional approach to identifying sites for feasibility studies is not agile enough to address the evolving nature of COVID-19.

The WG decided to form four subgroups to facilitate rapid execution of activities.

- Clinical Trial Network Inventory sub-WG (Inventory of networks and known capabilities)
- Survey Development sub-WG (Development of survey(s) and identification of target(s))
- Patient Population sub-WG (define patient populations)
- Innovations sub-WG (Identify innovations that will enable execution of CTs)

Overall, this WG will work in close consultation with the Therapeutics - Clinical WG.

Below is a summary of the key discussion themes.

Inventory of Clinical Trial Networks
In a parallel effort, National Institutes of Health (NIH) staff are developing an inventory of all NIH-funded CTNs, which will capture information about their capacity, locations, and patient populations. NIH is very interested in using the WG's input to shape the parameters of this inventory. For example, the WG may identify other non-NIH-funded networks such as PCORnet and clinical trial sites run by pharmaceutical companies or their contracted research organizations and academic centers.

The WG suggested that any inventory efforts should consider including groups that work outside the infectious disease space (e.g., cancer, cardiology) but have expressed interest in contributing to this effort or have a demonstrated capacity to study therapeutic interventions.

The WG discussed the relative importance of true clinical trial networks over single sites linked together in a multicenter trial, with a coordinating center and ancillary services, for just one specific trial. The WG agreed that the ability of such sites to pivot beyond a specific trial to new type of interventions would have to be evaluated on a case-by-case basis.

Define Patient Populations
To develop a useful inventory of CTNs and their characteristics, the WG must first determine the types of studies the CTNs will conduct (e.g., "decide the what before the how") in close coordination with the Therapeutics WG. Therefore, the WG decided that a next step will be to

define patient categories and their endpoints, which will inform development of a survey to collect information about network/site capacity. If patient categories are based on an ordinal scale for clinical improvement, then outcomes can be more easily envisioned and compared across studies. WG members suggested the following patient categories that could be amendable to master protocols: outpatient COVID-negative, outpatient COVID-positive, hospitalized, hospitalized and receiving CPAC, hospitalized and receiving mechanical ventilation or ECMO. It is likely that inpatient and critical care would be prioritized given the desire to repurpose therapies in those settings.

The WG agreed that pragmatic trials of repurposed (but not investigational) compounds with simple endpoints could be launched in a month's time. For example, in a study of COVID-positive outpatients, a simple endpoint could be hospitalization. Such pragmatic trials could result in quick answers for large populations.

Inventory of Clinical Trial Network Capacities

The WG agreed to conduct electronic surveys to ascertain network and site capacity in a two-pronged approach. First, to reduce burden on individual sites, the WG will survey the network Coordinating Centers, which will have basic information about, for example, the sites' data systems, data standards, patient populations, and access to reading centers and drug distribution centers. Second, individual sites can be surveyed for more nuanced data, such as numbers of cases and catchment areas, which may not be recorded by the Coordinating Centers and may differ by site based on the evolving nature of the epidemic.

WG members suggested collecting the following information about a site's capacity: patient participants, data management, regulatory environment, labs, linkages to health department and community, and methods to ensure safety (more of an investigational drug concern).

Networks with a strong infrastructure could be leveraged for their technology and relationships with sites to collate the surveyed information into a central database, perhaps through a portal as a way to reduce reporting burden on single sites.

Fit for Purpose and Quick Launch

Many networks are already fit for purpose to conduct trials in certain settings (e.g., PCORnet in outpatient settings). Still others are well positioned to launch new trials quickly (e.g., NIAIDS HIV/AIDS network). The factors that can predict launch readiness are existing contractual agreements, common data structure, data coordinating center, history of working together in different settings, and regulatory support. The WG agreed that available networks and sites that are clearly identified as fit for purpose and capable of a rapid launch should be tapped to start clinical trials as soon as possible, especially trials of repurposed drugs. Because the health care system is already stressed, it will be important to minimize the number of extra steps that a site must take to comply.

Innovation

Traditional public health reporting structures might not provide sufficient or timely information for effective response. By contrast, some websites are innovatively scraping and aggregating data from multiple sources to develop heat maps of COVID-19 prevalence (e.g., Maryland). While some people might question the validity of such data, this approach might be the best way to get a real-time picture of the disease spread. However, even innovative approaches to data collection may not adequately forecast the ebb and flow of the virus in waves for months to come. Therefore, rather than "chasing the epi," the WG agreed that it should cast a wide net—that is, add every possible site to the inventory that is fit for purpose and then filter down as outbreaks occur.

The WG also agreed that electronic health records (EHRs) are highly preferable to case report forms (which are more prevalent in single sites) as a means to collect data. As an added benefit, EHRs would enable off-site monitoring, which would limit exposure of monitors, patients, and clinical staff to the coronavirus. Other innovations include leveraging (1) the LabCorp registry to identify COVID-positive and -negative (and mostly outpatient) people for recruitment into trials and (2) networks that use e-consent (aka, no-touch consent) and telemedicine to engage participants who are remote from sites with capacity. Importantly, FDA has expressed a willingness to be flexible in its requirements about review and validation of software used in COVID-19 clinical trials, which will be an important consideration for researchers designing trials.

Challenges Specific to COVID-19 Clinical Trials
The WG members highlighted the following challenges specific to conducting COVID-19 trials:

- It will be difficult to identify participants for prevention trials, because the United States still does not have reliable or widespread testing. There are known issues with false-positives and false-negatives.
- Even sites deemed appropriate (e.g., ICUs) may be too overwhelmed to conduct a trial.
- Some sites might require that PPE and other needed materials and supplies are physically provided to them—rather than accepting the funds needed to purchase them as a budget line item.

Next Steps
The WG decided to form four subgroups to facilitate rapid execution of activities.

- Clinical Trial Network Inventory sub-WG (Inventory of networks and known capabilities)
- Survey Development sub-WG (Development of survey(s) and identification of target(s))
- Patient Population sub-WG (define patient populations)
- Innovations sub-WG (Identify innovations that will enable execution of CTs)

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Overall, this WG will work in close consultation with the Therapeutics - Clinical WG.

Appendix A: Participants List

WORKING GROUP MEMBERS

Lionel Bascles, PhD, *Senior VP, Global Head of Clinical Sciences & Operations, Sanofi*

Myron Cohen, MD, *Associate Vice Chancellor for Global Health and Medical Affairs, Director, Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill*

Larry Corey, MD, *President and Director Emeritus, Fred Hutch*

Elizabeth Desrosiers (Co-Chair), MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

James Dickens, *Program Manager, National Center for Advancing Translational Sciences*

James Doroshow, MD, *Director of the Division of Cancer Treatment and Diagnosis, National Cancer Institute*

David Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute*

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Michael Kurilla (Co-Chair), MD, PhD, *Director – Division of Clinical Innovation, National Center for Advancing Translational Sciences (NCATS)*

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Manizhe Payton, *Director, Office of Clinical Site Oversight, National Institute of Allergy and Infectious Diseases*

Laura Resnansky, *Vice President, Global Head of Clinical Operations – Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Genentech*

Badhri Srinivasan, *Head, Global Development Operations, Novartis*

Peter Stein, MD, *Director of CDER's Office of New Drugs, Food and Drug Administration*

Michael Vincent, MD, PhD, *Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

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INVITED PARTICIPANTS

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Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH*

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Rosa Alvarez*, Consultant, Deloitte*
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Elizabeth Kim*, Senior Consultant, Deloitte*
Benjamin Stratton*, Senior Consultant, Deloitte*
Brett Tolman*, Manager, Deloitte*
Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*
Jonathan Wachtel*, Manager, Deloitte*

Appendix B: Chat Transcript

From David Goff to Everyone 10:37

The 7 point ordinal scale could provide good outcomes for pragmatic trials

From Larry Corey to Everyone 10:42

The 2 NIAID prevention networks; the HVTN and the HPTN have done integrated trials and we have 45 US sites, 45 sub Saharan African sites and 20 South American sites all integrated with a common ability to conduct similar or complimentary trials.

From Larry Corey to Everyone 10:45

Is there an interest in reaching out to European

From David Goff to Everyone 10:45

Primary care practice-based research networks will be important to include. Some are funded by CDC, mostly through their prevention research centers program, others by NIH mostly through the CTSAs.

From Nayaksu to Everyone 11:04

Vendor considerations/innovations in the trials of new therapeutics context - consider remote monitoring capabilities

From David Goff to Everyone 11:11

Patient populations for master protocols could be considered in the context of the 7-point ordinal scale, adding out-patient/uninfected for prevention and vaccine trials.

High-Level Meeting Summary

The Vaccines Working Group (WG) convened to hear presentations from Drs. Trevor Bedford and Jesse Bloom on their investigations into emerging SARS-CoV-2 variants, to inform implications for vaccine development.

Molecular Evolution of SARS-CoV-2

Dr. Trevor Bedford, Fred Hutchinson Cancer Research Center

Tracking in Real Time

NextStrain.org tracks viral genetics in real time using GISAID (currently approximately 510,000 viral genomes shared) to identify emerging SARS-CoV-2 variants. Using these resources, Dr. Trevor Bedford and colleagues visualized how SARS-CoV-2 spread within Wuhan, China during 2019 and eventually to Europe and North America. During early 2020, different global viral lineages, including those with early mutations like D614G, began arising within different countries and some of these variants displayed transmissibility advantages, facilitating their more rapid spread.

Emergence of Variants of Concern

Variants with substitutions in the spike at 484K and 501Y began emerging during the Fall of 2020 repeatedly across the world; variants with one or both substitutions now account for approximately 35 percent of COVID-19 cases globally and that percentage continues to rise. Emerging in the UK during September 2020, the 501Y.V1 variant (also called B.1.1.7) has accumulated multiple mutations, including the ORF1ab 3675-3677 deletion, multiple spike protein deletions, and an ORF8 27* knockout. The 501Y.V2 (or B.1.351) variant emerged in South Africa and has quickly become the dominant strain within that country. Similarly to 501Y.V1, 501Y.V2 has accumulated many mutations, including the same ORF1ab deletion and multiple spike protein substitutions; many of these mutations are likely to impair antibody binding. The 501Y.V3 (P.1) emerged in Brazil, specifically in the Amazonas region; this variant also includes the ORF1ab 3675-3677 deletion and multiple spike protein deletions.

In observing these three variants' emergences, all show a larger number of mutations than expected from the steady rate of accumulation previously observed and they share a number of mutations in common. Given this, there is a hypothesis that these variants derive from rare events of viral evolution during chronic infection under immune pressure. Dr. Bedford presented an example of an immunocompromised patient with a persistent infection who was receiving convalescent plasma. Between Day 18 and Day 152, this patient's viral strain evolved to include both 484K and 501Y, suggesting that single persistent infections can produce viral variants that are emerging globally.

Expectations for Antigenic Evolution

Dr. Bedford and colleagues anticipated that SARS-CoV-2 would evolve similarly to seasonal coronaviruses, such as OC43 (which displays adaptive evolution and antigenic drift). Other viruses also display adaptive evolution, including influenza, whereas some viruses do not (e.g., measles); most adaptive evolution is observed within the receptor-binding domain (RBD).

SARS-CoV-2 has steadily accumulated approximately one mutation every two weeks since the beginning of the pandemic. The total number of amino acid changes in the variants of concern is only slightly above the overall trend; however, the variants of concern have substantially more amino acid substitutions in S1 (~8-10) compared to the basal evolution (~2-4). The basal S1 evolution in SARS-CoV-2 (2.9 substitutions per year) is similar to influenza A (~1.5-2.5 per year in HA1) and well above influenza B (~0.5-0.7 per year). Amino acid substitutions can't be immediately converted to antigenic drift, but influenza subtypes show a correlation between the rate of substitutions and the rate of antigenic drift measured by hemagglutinin inhibition assays. The 501Y.V2 variant displays an 8-fold reduction in neutralization titer, which is equivalent to 3 years of H3N2 evolution. Whether this rate of change will be sustained, or whether viral evolution has converged to an equilibrium, is unknown.

Current US Circulation Patterns

Before February 2021, genomic surveillance within the U.S. was not sufficient, in particular with long lags between specimen collection and sequence availability. As of February 2021, viral sequencing lag has dramatically decreased, with ~7,000 sequences submitted for samples collected in the past 30 days (in comparison to ~100 sequences from samples collected in the past 30 days prior to January, while the rate of sample collection has been relatively steady). Sampling within the US is geographically concentrated, and surveillance could be further improved by more distributed sampling.

Thus far, the U.S. does not yet have an endogenous variant of concern. The 20C/S:452R variant emerged in Sothern California and has increased in prevalence, but the rate is much slower than the rates at which the 501Y.V1 and 501Y.V2 variants took over in the UK and South Africa. The 501Y.V1 variant has travelled to the U.S. and is increasing in prevalence more rapidly; Dr. Bedford suggested that the 501Y.V1 variant will dominate cases within the U.S by the end of March, with a rise in the V2 and V3 variants as immune pressure increases in summer or fall.

Interpreting the Evolution of SARS-CoV-2

Dr. Jesse Bloom, Fred Hutchinson Cancer Research Center

Viral Escape and Evolution

Only certain viruses can evolve in a manner that erodes antibody immunity and facilitates escape. For example, the measles virus has not evolved to escape immunity, whereas the influenza virus can do so (requiring the vaccine to be updated annually). The evolution of seasonal CoVs has been studied by measuring the neutralization titer of serum from natural infection against viral isolates from other years. Serum from CoV-229E infection typically neutralizes contemporaneous virus well, but shows substantially reduced neutralization against later (and sometimes earlier) isolates. However, this pattern varies significantly across samples, with some sera showing effective neutralization over 20+ years of viral evolution. These observations show that the rates at which viral evolution erodes antibody immunity differ across individuals (probably because of differences in epitope specificity). The basis for the differences in neutralization durability are being studied to inform how to design vaccines to elicit evolution-resistant responses.

Similar to SARS-CoV-2, most CoV-229E mutations arise within the RBD (and to a lesser extent the NTD), particularly in the receptor binding loops. For SARS-CoV-2 most neutralizing activity is facilitated by RBD-binding antibodies (as shown through RBD-binding depletion experiments). Thus, Dr. Bloom and colleagues sought to investigate the effects of SARS-CoV-2 RBD mutations on three biochemical phenotypes that contribute to viral fitness: (1) RBD folding, (2) RBD-ACE2 binding, and (3) antiviral antibody binding to RBD. In order to survive, SARS-CoV-2 must continue to fold RBD properly and bind to ACE2 with high affinity while evolving to escape antibody binding.

Escape Mutations and Antibodies

To study RBD mutations, Dr. Bloom and colleagues used a barcoded yeast display model with fluorescent tagging of RBD and ACE2 to assess a wide range of RBD mutations. Characterization of mutations by expression of (properly folded) RBD and ACE2 binding shows that some commonly observed amino acid substitutions (e.g., 501Y, 484K, 452R) increase ACE2 binding affinity, which may be related to their increasing epidemiological prevalence. It is possible that the virus will "use up" improvement to ACE2 binding affinity and that aspect of evolution will slow down.

RBD variants are also screened for escape from binding antibodies (monoclonal and polyclonal) to identify mutations that confer particularly strong escape. To test if the phenotypic escape map explains the virus's evolution, Dr. Bloom and colleagues studied how SARS-CoV-2 grew in culture in the presence of the COV2-2499 mAb and identified escape mutations (G446D and Q498R) that were able to reduce antibody binding within 5 of 16 viral replicates. Those two mutations did not stand out in the antibody escape screening until the results of that screen were filtered down to single-nucleotide mutations that maintained high affinity ACE2 binding.

Dr. Bloom and colleagues replicated these findings using a variety of other binding mAb antibodies, demonstrating that the mutations selected in culture matched those that were characterized as single-nucleotide, high ACE2 binding affinity, and strong escape from binding antibodies. Thus these screens may predict the mutations that are likely to arise under specific pressure. For one mAb, COV2-2165, no escape mutations were identified in 56 attempts, and for that mAb all of the single-nucleotide escape mutants showed reduced expression of properly folded RBD and/or reduced ACE binding affinity; i.e., these experiments did not identify an evolutionarily accessible escape mutant. These experiments have been repeated including mAbs that are in clinical development.

Polyclonal Antibodies

Polyclonal antibodies can bind to multiple epitopes, making polyclonal responses potentially more resistant to escape. How true this is depends on the specifics of the response. For example, polyclonal responses against influenza are often highly focused on an immunodominant epitope, enabling single mutations to reduce neutralization more than 10-

fold. Measles offers a contrast, with polyclonal responses against multiple epitopes that limit the effect of any single mutation.

To assess the impact of polyclonal antibodies against SARS-CoV-2, Dr. Bloom and colleagues used the yeast display system to identify mutations that escaped binding by convalescent human sera. Different sera selected for substitutions at different amino acids, and differed in their degree of focusing. Based on results across sera, the receptor-binding ridge, in particular at E484 (which is mutated in the 501Y.V2 and 501Y.V3 lineages), appears to be the most prevalent binding region, and the 443-450 loop is the next most prevalent. The phenotypic differences observed across patients validate neutralization assays, which found that sera showed reduced or abrogated neutralization against viral mutants identified in the escape experiments.

Plotting the average escape of site mutations against polyclonal sera against the prevalence of mutations at that site in surveillance samples clearly identifies the 484 site as one of high concern due to its high facilitation of escape and high population prevalence. That comparison identifies additional epitopes that confer significant escape potential and could rise in prevalence if E484 mutations are controlled.

Discussion

Observed and predicted viral evolution

Dr. John Mascola asked if there is a hypothesis to explain the ubiquity of the ORF1 knock-outs across the variants of concern. Dr. Bedford suggested that it could be related to an interferon response, but that he doesn't know of a good hypothesis.

Dr. Jay Grobler asked whether any sequence change within the California variant can be associated with its recent expansion within the U.S. Dr. Bedford noted that the California variant contains the 13I, 152C and 452R mutations, which are likely contributing to its expansion, and added that the 452R mutation is also appearing independently in other U.S. strains.

Dr. Carl Dieffenbach asked whether there are any expectations about recombination events enabling a fitter spike protein. Dr. Bedford noted that an abundance of evidence exists that recombination is occurring in seasonal coronaviruses, which is largely related to shedding deleterious load across the viral genome. Recombination within the spike protein may be unlikely, and unnecessary to discover improved spikes given that the virus mutates rapidly enough, but recombination may start to be observed with increases in co-infection.

Dr. Nancy Sullivan asked about the sequences or rate information used to predict a variant's future dominance within a population. Dr. Bedford noted that the best method to predict dominance is to map mutation prevalence over time and use biological priors (like the presence of E484 and Y501 mutations) to identify variants to watch more closely. He added that early identification of variants of concern that don't exhibit previously identified important mutations will be challenging.

Dr. Mary Marovich asked why 501Y.V1 / B.1.1.7 is predicted to predominate over other variants, such as the 501Y.V2 / B.1.351. Dr. Bedford noted that travel connections play a role, but the prediction is primarily based on the observations of how quickly the variants have spread after they establish in a new location. The intensity of the epidemic in South Africa may have facilitated a particularly rapid rise in V2's prevalence there.

Dr. Doug Lowy asked how much concern should be attached to the potential of new variants evolving in response to the rising prevalence of natural and vaccine-induced immunity in places like the US. Dr. Bedford noted that the 501Y.V1 / B.1.1.7 variant will likely be dominant within the U.S. by the end of April, but that the combination of natural immunity, vaccination, and seasonal effects will control infection incidence over the summer. Although difficult to predict, the fall may offer the opportunity for a variant to emerge and spread.

Dr. John Mascola asked whether punctuated evolution is occurring. Dr. Bedford noted that whether punctuated evolution will occur for SARS-CoV-2 is currently unknown. Evolution is generally quite punctuated for influenza A, but the 2009 emergence of H1N1 showed steady evolution.

Experimental evaluation of the implications of viral mutation

Dr. Michael Diamond asked whether Dr. Bloom had completed depletion and neutralization assays with viruses produced within different cell types (e.g., Vero vs. Vero-TMPRSS2) and targeting different cells types (e.g., Vero vs. Vero-hACE2) because of observations that these choices produce substantial differences in neutralization and RBD dependence. Dr. Bloom noted that his experiments were performed using pseudoviruses on ACE2-overexpressing cells, noting that this has implications for the apparent relative importance of RBD vs. NTD binding. Even if the experiments over-represent the importance of RBD, extrapolation from CoV-229E also suggests that RBD is likely to be the most important site for antibody binding.

Dr. Rick Higgs asked whether the yeast model's RBD is primarily in the open or closed conformation. Dr. Bloom noted that the RBD is in the open conformation because the rest of the spike protein is not present. Consequently, these experiments may overemphasize the importance of binding to the epitopes accessible in the open conformation.

Dr. Diamond asked about ACE2 affinity changes related to K417N. Dr. Bloom noted that K417N alone decreases ACE2 affinity. That change may be counterbalanced by a mutation like 501Y, or there may be interactions among multiple mutations in the RBD that are not predicted from evaluating individual mutations. Dr. Diamond also asked about the role of other receptors and attachment factors. The availability data have not motivated investigation of these yet, but it was agreed that experiments could be done to look for viral variants selected in culture with cells that do not express ACE2.

Dr. Ryan Connor asked whether compensatory mutations will play a major role in SARS-CoV-2 evolution. Dr. Bloom confirmed that epistasis could occur among mutations, particularly those related to counterbalancing changes in ACE2 affinity (e.g., as may be implied by the co-occurrence of 501Y and K417N), but noted that conformational epistasis may become important as mutations accumulate.

Implications for protection from natural and vaccine-derived immunity

Dr. Larry Corey asked if there is an in vitro experiment that could help determine whether initial antigenic exposure influences the robustness of the resulting immune response to viral evolution. Dr. Bloom noted sequential infections (in animal models or in human natural history) may provide insight, and that this could produce a broadening of the response or potentially show a deleterious effect (e.g., repeated flu vaccination results in decreased immunity). He added that the diversity of epitope targeting in the population will likely increase over time as the virus evolves and individuals experience different exposures, which may be beneficial control at the population level.

Dr. Peter Dull asked when researchers will have access to data on how well responses to V2 infection neutralize the ancestral SARS-CoV-2 strain. Dr. Bloom noted that these data are important to understanding the risks of shifting vaccination to focus on V2. Dr. Bedford shared that in ferret models of flu, asymmetries in cross-neutralization are observed between responses raised against different strains [possibly suggesting that because responses against the ancestral strain don't neutralize V2 well doesn't guarantee that responses that neutralize V2 won't neutralize the ancestral strain well].

Dr. Ann Arvin asked about the systems in place to evaluate breakthrough infections (against either natural or vaccine-derived immunity) that progress to disease. Dr. Bedford noted that one of the biggest shortcomings in genomic surveillance in the US is the lack of connection between viral samples, vaccination status, and patient outcomes.

Dr. Gregory Glenn noted that in their South Africa trial, Novavax found no impact of baseline seropositivity on the incidence of subsequence infection in either the placebo arm or the vaccine arm (which showed 50% efficacy); this result does not depend on IgG titer against the ancestral strain. Baseline seropositivity (which was 30%, unexpectedly high) is presumed to be due to infection with an ancestral strain based on the timing of the start of the study. This reinforces the hypothesis that immune pressure has led to the evolution of V2 and that herd immunity based on ancestral strain infection may not be effective at stopping transmission if V2 were to spread more widely.

For the Novavax UK trial (which started as the V1 variant became more prevalent), vaccine efficacy was observed to be higher against ancestral variants than V1, consistent with observed differences in neutralization titers of vaccinee sera against ancestral vs. V1 strains; similar data are not available for South Africa and V2 yet, but Dr. Glenn predicted an analogously concordant comparison between observed efficacy and neutralization (after correcting for confounding due to the effect of HIV infection). Dr. Bloom observed and Dr. Mascola agreed that the question of whether mis-matched immune responses are still sufficient to prevent serious outcomes such as hospitalization and death is a crucial and open question. Dr. Roland Zahn commented that the J&J trials appear to show consistent protection against the most severe outcomes across regions; Dr. Dull observed that across all the efficacy studies globally, there is still a very low rate of breakthrough infections leading to serious disease outcomes. Dr. Glenn pointed out that the current observations are in the most optimistic interval, shortly after vaccination, and that immunity is expected to wane over time. This may require establishing immunity to V2 in the fall.

Next Steps

Dr. Santos will soon share with Vaccines WG members calendar invitations to upcoming Vaccines WG meetings, as well as the slides presented during today's meeting (which can be found here and here).

Appendix A: Participants List

WORKING GROUP MEMBERS

Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI), National Institutes of Health (NIH)*

Paula Annunziato, MD, *Vice President, Vaccine Clinical Development, Merck*

Ann Arvin, MD, *Professor of Pediatrics and Microbiology & Immunology, Stanford University*

Susan Buchbinder, MD, *Director of Bridge HIV, San Francisco Department of Public Health, and Professor, UCSF*

Larry Corey, MD, *Professor and Principal Investigator, University of Washington and HIV Vaccine Trials Network, and Past President and Director, Fred Hutchinson Cancer Research Center*

Marco Cavaleri, PhD, *Head of Biological Health Threats and Vaccines Strategy, European Medicines Agency (EMA)*

Gregory Glen, MD, *President, Research and Development, Novavax*

Barton Haynes, MD, *Director, Human Vaccine Institute, Duke University School of Medicine*

Peter Hotez, MD, PhD, *Dean for the National School of Tropical Medicine, Baylor College of Medicine, and Director, Texas Children's Center for Vaccine Development*

John Mascola, ***MD****, Director, Vaccine Research Center, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Nelson Michael, MD, PhD, *Director, Center for Infectious Disease Research, Walter Reed Army Institute of Research*

Paul Offit, MD, *Professor, University of Pennsylvania, and Director, Vaccine Education Center, Children's Hospital of Philadelphia*

Michael Santos, PhD, *Associate Vice President, Science, Foundation for the NIH (FNIH)*

Hanneke Schuitemaker, PhD, *Global Health, Viral Vaccine Discovery and Translational Medicine, Johnson & Johnson's Janssen Vaccines*

Brett Tolman, MA, *Strategy Manager, Deloitte*

INVITED PARTICIPANTS

Michael Abram, PhD, *Translational Medicine Lead, Infectious Diseases, Head, Clinical Virology and RSV Surveillance, Astra Zeneca*

Trevor Bedford, PhD, *Associate Professor, Vaccine and Infectious Disease Division and Basic Sciences Division, Fred Hutchinson Cancer Research Center*

Lisa Marie Bentley, *BARDA*

Jesse Bloom, PhD, *Associate Professor, Public Health Sciences Division and Basic Sciences Division, Fred Hutchinson Cancer Research Center*

Helen Bright, PhD, *Director of Virology, Biopharma R&D, AstraZeneca*

Paula Bryant, PhD, *Director, Office of Biodefense, Research Resources and Translational Research, NIAID*

Myron Cohen, MD, *Director for Global Health & Infectious Diseases, University of North Carolina (UNC) School of Medicine*

Ryan Connor, PhD, *NCBI*

Michelle Culp, BSN, MPH, *Senior Advisor, Office of Science Policy, NIH*

Michael Diamond, MD, PhD, *Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University*

Carl Dieffenbach, PhD, *Director of the Division of AIDS, NIAID*

Filip Dubovsky, MD, MPH, *Senior Vice President and Chief Medical Officer, Novavax*

Peter Dull, MD, *Deputy Director, Integrated Clinical Vaccine Development, Global Health Division, Bill and Melinda Gates Foundation*

Richard Eastman, PhD, *Biologist, NCATS*

Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, NIAID, NIH*

Clint Florence, PhD, *Program Officer, Research Resource Section, OBRR, DMID, NIAID, NIH*

Ellen Gadbois, PhD, *Program Lead, Biosafety, Biosecurity, and Emerging Biotechnology Policy Division, Office of Science Policy, NIH*

Paul Gillard, MD, *Senior Director, Clinical Development, GlaxoSmithKline (GSK)*

Jay Grobler, PhD, *Executive Director, Infectious Disease Biology, Merck*

Rajesh Gupta, MD, MPH, *Vice President, Global Health Portfolio and Public-Private Partnerships, VIR*

Holli Hamilton, MD, MPH, *Senior Medical Officer, BARDA*

Judith Hewitt, PhD, *Deputy Director, Office of Biodefense, Research Resources and Translational Research, NIAID*

Rick Higgs, MS, *Senior Research Fellow, Eli Lilly*

Yun Ji, PhD, *Director, Research and Translational Sciences, Brii Biosciences*

Nicole Kallewaard, *Microbial Sciences, BioPharmaceuticals R&D, AstraZeneca*

Joanne Lumsden, PhD, *Senior Scientific Program Manager, Drug Development Partnership Programs, NCATS, NIH*

David Margolis, MD, MPH, *Vice President, Head of Infectious Diseases, Brii Biosciences*

Mary Marovich, MD, *Director, Vaccine Research Program, NIAID, NIH*

Kathy Neuzil, MD, MPH, FIDSA, *Director, Center for Vaccine Development and Global Health, University of Maryland School of Medicine*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Kim Pruitt, PhD, *Chief, Information Engineering Branch, National Center for Biotechnology Information, National Library of Medicine*

Stephen Sherry, PhD, *Acting Director, National Center for Biotechnology Information, National Library of Medicine*

Alex Sigal, PhD, *Group Leader and Assistant Investigator, Max Planck Institute for Infection Biology*

Mark Sotir, PhD, *Epidemiologist, CDC*

Nancy Sullivan, PhD, *Senior Investigator and Chief of the Biodefense Research Section, Vaccine*

Research Center, NIAID, NIH
Jenny Svarovskaia, PhD, *Senior Director, Clinical Virology, Gilead Sciences*
Kanny Wan, PhD, *Research Scientist, NCATS*
Li Yan, MD, PhD, *Chief Medical Officer, Brii BioSciences*
John Young, PhD, *Global Head Infectious Diseases and Vice President, Roche*
Roland Zahn, PhD, *Senior Scientific Director, Preclinical Immunology, Viral Vaccines, Janssen*
Qing Zhu, PhD, *Senior Vice President, Brii Biosciences*

FNIH STAFF
Stacey Adam, PhD, *Director, Cancer, FNIH*
Stephanie James, PhD, *Senior VP of Science, FNIH*

Bethany Stokes, MS*, Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From John Mascola to Everyone: 11:40 AM

so still no good hypothesis for ORF1 KO?

From Peter Hotez to Everyone: 11:53 AM

Now that UK, ZA, BR are in US, do you see one dominating the other?

From Jay Grobler to Everyone: 11:54 AM

Were there any additional sequence changes noted in the California variant associated with its more recent expansion?

From Carl Dieffenbach to Everyone: 11:55 AM

Any predictions/thoughts on possible recombinants as a way of hitting a fitter S glycoprotein?

From Doug Lowy to Everyone: 11:55 AM

How much concern should we have about the possible development of new variants as a higher proportion of the US population has antibodies from prior infection or vaccination?

From Nancy Sullivan to Everyone: 11:56 AM

How many occurrences (or at what rate?) do you need to form your expectation that a variant will become dominant.

From Jesse Bloom to Everyone: 11:57 AM

Here are my slides: https://slides.com/jbloom/sars-cov-2_activ

From Peter Hotez to Everyone: 11:58 AM

Just want to also say thank you to Trevor and Jesse for their important work and contributions to public health

From John Young to Everyone: 11:59 AM

Trevor, great presentation! Thank you. Would it be possible to get your slide deck also?

From Barton Haynes, M.D. to Everyone: 11:59 AM

agree. wonderful presentation. slides would be great!

From Trevor Bedford to Everyone: 12:04 PM

Thanks John. My slide deck is available at https://bedford.io/talks/sars-cov-2-molecular-evolution-activ/. Please feel free to share.

From Michael Diamond to Everyone: 12:04 PM

Have you done these depletions and neutralization assays with virus produced on different cells (Vero vs Vero-TMPRSS2)_ and using different target cells (Vero vs Vero-hACE2) — we have seen substantive differences in neutralization and RBD dependence

From Rick Higgs to Everyone: 12:05 PM

Do you have any data on whether the RBD on yeast are primarily in the open or closed conformation?

From Michael Diamond to Everyone: 12:06 PM

what happens with K417N and ACE2 affinity?

From Kim Pruitt to Everyone: 12:09 PM

@Jesse will you be able to share your slides? (both presentations excellent and information rich!)

From Michael Diamond to Everyone: 12:15 PM

There are a lot of other reported/putative attachment factors/receptors....how does this impact the analysis

should we be repeating the VSV escape selection on hACE2-deficient cells

From Larry Corey to Everyone: 12:25 PM

is there an invitro experiment tht can help define whether original antigenic exposure to a single versus 'bivalent variant ends up with better " stability against escape variants

From Peter Dull - BMGF to Everyone: 12:26 PM

not necessarily a question for Jesse/Trevor but when will we have cross-neuts data from convalescents in RSA/Brazil on our ancestral strain?

From Mary Marovich to Everyone: 12:26 PM

why would B117 be predicted to dominate first - before B1351 (E484), just that the former arrived in US first?

From John Mascola to Everyone: 12:28 PM

is punctuated evolution occurring and any prediction on when/if it slows down?

From Ann Arvin to Everyone: 12:29 PM

How much of a concern should we have about infection/vaccine immunity shaping viral evolution? What systems are in place to prepare for collection of isolates for genomics when breakthrough infections actually associated with disease occur in vaccine recipients or previously infected people?

From Gregory Glen to Everyone: 12:30 PM

In South Africa, we (NVAX) found there was no impact on the rate of V2 infections in those who were seropositive, presumably due to the previous Wuhan-like prototype...this reinforces the hypothesis that immune pressure has led to V2 in the field and suggests that herd immunity due to infection with prototype may not be effective if V2 were to widely spread. The placebo AR was 3.9% in both seropositive and seronegative. This seems worrisome for the future places where there is not V2 herd immunity?

From Ryan Connor to Everyone: 12:30 PM

for Jesse - is the data underlying the heatmaps and scatter plots public? how likely do you think it is that compensatory mutations could significantly alter your results?

From Jesse Bloom to Everyone: 12:31 PM

Yes, the heat maps etc are all linked to in my slides, which are here: https://slides.com/jbloom/sars-cov-2_activ

From Peter Hotez to Everyone: 12:42 PM

Thank you for great presentations today

From Gregory Glen to Everyone: 12:46 PM

Great presentations....!!!

From Kim Pruitt to Everyone: 12:46 PM

Will the recording be available for others to listen to?

From John Mascola to Everyone: 12:46 PM

thank you Jesse and Trevor!

From Roland Zahn to Everyone: 12:46 PM

agree, thanks for the great presentations!

From Trevor Bedford to Everyone: 12:46 PM

Thanks all

High-Level Meeting Summary

The Vaccines Working Group (WG) convened to hear presentations from Drs. Penny Moore and Alex Sigal on their work studying the South African SARS-CoV-2 variants and a presentation from Dr. Joe Menetski detailing ACTIV's efforts to evaluate emerging variants.

Immune Responses to 501Y.V2

Penny Moore, PhD, Wits, National Institute of Communicable Diseases, and CAPRISA

Neutralization Titers Against Ancestral and New Variants

The South African variant 501Y.V2 contains three mutations in the receptor binding domain (RBD; N501Y, E484K, and K417N) and four mutations in the N-terminus domain (NTD; L18F, R246I/Δ242-244, D80A, and D215G); these mutations are common amongst many emerging variants of concern. Dr. Moore's team used a lentivirus-based pseudovirus neutralization assay in 293T cells that overexpress ACE2 to evaluate neutralization titers against D614G (the ancestral variant), 501Y.V2, and a triple RBD mutant viruses. First, they assessed 44 donor plasmas collected during the first COVID-19 wave in South Africa (D614G infection) and found that 50 percent of samples displayed titers above 400 against D614G. When those sera were assayed against 501Y.V2, titers reduced by 13-fold on average and 48 percent of samples lost neutralizing activity (titers <50). Donors that exhibited higher titers against D614G typically retained higher titers against 501Y.V2 and the donors with lower titers against D614G resulted in lower titers against 501Y.V2. Neutralization titers were on average 5-fold lower against the triple RBD mutant than against D614G, an intermediate result showing that the RBD mutations are the most important factor in decreased neutralization, but NTD mutations also plays a role in reducing titers.

501Y.V2 and Vaccine Efficacy

In collaboration with Dr. Alex Sigal, Dr. Moore evaluated vaccine efficacy against 501Y.V2 in order to assess possible corelates of protection. Efficacy trial enrollment in South Africa occurred as 501Y.V2 became prevalent and the 501Y.V2 variant was responsible for more than 90 percent of each vaccine trial's infections. Vaccine efficacies were markedly lower in South Africa's vaccine trials compared to those in US, UK, and Brazil for the three vaccines studied: Janssen (57 compared to 72 percent), Novavax (49 [60 in HIV- participants] compared to 90 percent), and AstraZeneca (22 compared to 70 percent). This finding suggests that the vaccines have a significantly lower efficacy against the new variant. Janssen has reported that its vaccine generates 85 percent efficacy against severe disease caused by 501Y.V2, whereas the other trials have not yet reported this information. Currently, introduction of the AstraZeneca vaccine has been suspended due to concerns related to diminished efficacy against the new variant.

Dr. Moore further investigated the effect of 501Y.V2 mutations on neutralization titers for 25 AstraZeneca trial participants: 19 who received vaccine, 6 of which were also infected, and 6 who received placebo and were infected). As described previously, the sera from these participants were assayed for neutralization against D614G, the triple RBD variant, and 501Y.V2. All subgroups showed the highest titers against D614G, substantially lower titers against the RBD variant, and further reduced titers against 501Y.V2. By contrast, levels of antibody binding to D614G and 501Y.V2 were relatively similar for vaccine-induced responses and natural infection (typically only 1-3x lower against 501Y.V2 than D614G) – this may be important when considering correlates of protection for severe disease. In addition to these results on the decreased neutralization of vaccine-induced and D614G-infection-induced immune responses against 501Y.V2 compared to D614G, separate studies not shown in the meeting have found a similar result for 3 classes of therapeutic mAbs.

Immune Response to 501Y.V2 infection

Dr. Moore and her team sought to investigate immune responses due to 501Y.V2 infection, particularly in comparison to the ancestral variant and related to cross-reactivity in binding and neutralization. To investigate these responses, they partnered with the University of Cape Town to analyze 100 samples taken in January from acute hospitalized patients at Groote Schuur Hospital (GSH; samples have not yet been sequenced to confirm 501Y.V2, but approximately 90 percent of all cases in South Africa were 501Y.V2 at time of collection). Sera from 501Y.V2 infections show similar binding against D614G and 501Y.2 (measured both against the RBD and a stabilized [HexaPro] spike protein). The putative 501Y.V2 hospitalized cohort showed similar levels of binding and neutralization against 501Y.V2 as a cohort from June-July 2020 (putatively D614G infection) showed against D614G. (A cohort with mild or moderate disease [putatively D614G] displayed significantly lower levels of both binding and neutralization against D614G than the hospitalized cohorts showed against their homologous viral strains. A similar comparison for samples from mild or moderate 501Y.V2 disease is planned.)

Dr. Moore analyzed samples from 20 cases of disease due to 501Y.V2 for neutralization against D614G, the triple RBD variant, and 501Y.V2. On average, sera raised against 501Y.V2 infection neutralize 501Y.V2 well (~80% above titers of 400), the RBD variants almost equally well, and the D614G variant less well (~3-fold lower titers against D614G than against 501Y.V2). In both relative and absolute comparisons, the neutralization of D614G sera against 501Y.V2 is worse than then neutralization of 501Y.V2 sera against D614G.

Discussion

Dr. Larry Corey asked whether any investigators are evaluating immune responses to NTD mutations. Dr. Moore noted that different patterns are observed in sera from 501Y.2 infection: some samples show lower neutralization against the RBD variant than against 501Y.V2, showing that NTD mutations play a role in the difference in neutralization observed between 501Y.2 and D614G (though most of the difference appears to be to RBD mutations); other samples show *better* neutralization against the RBD variant than against 501Y.2 or D614G (implying that 501Y.V2 sera have better NTD responses against WT NTD than against the mutated NTD seen in the infection – this is not explained). Overall, Dr. Moore believes that response against RBD is the most important, but further research to understand immunodominance is ongoing.

Dr. Vivek Shinde noted that in (b) (4) trial vaccine efficacy was 60% in the 95% of the participants who did not have HIV (49% efficacy is for the combined population regardless of HIV status); 501Y.V2-specific efficacy will be reported and will be similar. (b) (4) trial participants were ~30 percent seropositive at baseline (based on an assay with good performance). Seropositivity, which was assumed to be caused by infection with pre-501Y.V2 virus, did not appear to provide any protection participants in the placebo arm from mild disease (not all infections have been sequenced, but of those that have >90% are 501Y.V2); currently there are not enough data to respond about more serious disease endpoints.

In the chat, Dr. Peter Hotez asked whether the observation that lower neutralization titers against D614G do not appear to protect against 501Y.V2 (because of their low neutralization) had implications for vaccines that elicit lower levels of nAbs. In response, Dr. Corey commented that other immune responses, such as T cell, will be important to understanding differences in protection against different strains. Dr. Moore agreed that measures other than antibody neutralization are needed to assess changes in vaccine efficacy and noted that the field currently relies heavily on antibody titers to assess post-vaccine samples. Dr. Sigal concurred and added that the observation that antibody binding varies much less across strains than neutralization does suggest that other routes of immunity are less affected by variants, which is also likely to be true of T cell–mediated immunity (because of the wider range of natural variation in cellular immune responses); this suggests that neutralization is an important correlate of protection from infection [but leaves open the question about other endpoints].

Dr. Paul Offit asked whether there is a case in which a patient who has received the vaccine or recovered from infection with D614G has been subsequently infected with 501Y.V2 and experienced a more severe disease phenotype. Dr. Moore noted that very little information is known about this situation and most that exists is anecdotal. Dr. Shinde noted that the accumulation of addition data from vaccine trials should inform whether natural immunity against D614G modifies disease severity due to 501Y.V2 infection in the placebo groups.

Cross-Neutralization of Plasma Elicited by 501Y.V2 Versus Earlier Variants

Alex Sigal, PhD, Africa Health Research Institute

Overview

South Africa experienced two waves of infection, the first corresponding to D614G and the second to 501Y.V2. Today, 95 percent of infections are caused by 501Y.V2. Dr. Sigal and his team have collected swabs and blood samples from both the first and second waves from healthcare facilities capturing to mild, moderate, and severe/ICU cases. These samples are used to sequence and outgrow virus and measure plasma neutralization of virus using live-virus neutralization assays. These assays plate Vero E6 cells in a monolayer with virus and a plasma dilution and count foci.

Dr. Sigal presented a video depicting cells overexpressing ACE2 under normal conditions and upon infection with D614G; after two days, all cells infected with live virus died. The lab has grown out two viral strains (501Y.V2 / B.1.135 from Nov 2020 and B.1.1.84 from Jun 2020) and has many plasma samples raised against multiple different sequenced strains. One plasma sample from Oct 2020 showed the E484K mutation, but otherwise samples from the 1st wave did not show mutations characteristic of 501Y.V2 (though they did show differences from each other). All of the sequenced samples from the second wave were 501Y.V2.

Live Virus Neutralization: Homologous Neutralization and Cross-Neutralization

Live-virus neutralization assays were performed across the 4 combinations of 1st- and 2nd-wave plasma and 1st- and 2nd-wave virus. Plasmas neutralize homologous virus (virus from the same wave but sampled from a different individual) relatively well. D614G plasmas neutralize 501Y.V2 virus poorly, whereas 501Y.V2 plasmas neutralize D614G virus almost as well as D614G plasmas neutralize D614G virus, though not as well as 501Y.V2 plasmas neutralize 501Y.V2 virus. These results are summarized here in NT_{50}:

	1st-wave plasma	2nd-wave plasma
1st-wave virus	344	150
2nd-wave virus	41	620

Overall, 2nd-wave plasma performs very well against 2nd-wave virus and reasonable well against 1st-wave virus. An important caveat to these conclusions is the possibility that participants from whom the second-wave samples were taken had also previously been infected with first-wave virus. The clinical team conducted interviews with its 2nd-wave sample donors and confirmed that none had a history of previous SARS-CoV-2 infection; in addition, none of the donors appeared in the registry of previously infected individuals. Overall, it is unlikely that previous infection explains the relatively good performance of 2nd-wave plasmas against 1st-wave virus.

Discussion

Dr. Ann Arvin asked whether there is any relationship between the data presented in this meeting and the decline in COVID-19 incidence in South Africa (the apparent end of the 2nd wave). Dr. Moore thinks that it is unrelated and unexplained, as was the drop in incidence at the end of wave 1.

ACTIV TRACE

Joseph Menetski, PhD, Foundation for the National Institutes of Health

The Preclinical WG launched the Tracking Resistance and Coronavirus Evolution (TRACE) WG to assess how ACTIV could address emerging variants of concern through the following aims:

- Coordinate data, resources, and recommendations to ensure the generation of rapid and comparable results
- Prioritize variants based on threat-level assessments
- Validate the therapeutic impact of priority variants

- Rapidly disseminate results to ensure optimal use by the research and development community to fight the pandemic

The main goal of the TRACE effort is to ensure that generated data are used efficiently to develop in silico predictions that may help evaluate therapeutic impact and escape capabilities of specific variants and to prioritize additional preclinical studies (while researchers wait for human data). Dr. Menetski presented the current TRACE WG workflow (summarized below), noting that Step 1 is primarily performed in the US by the CDC. He added that the TRACE WG aims to standardize all results of these steps and eventually disseminate weekly progress reports.

- Step 1: Monitor global emergence and circulation of SARS-CoV-2 mutations
- Step 2. Cross-reference against databases of experimentally and clinical phenotyped mutants
- Step 3: Characterize variants via in vitro critical-path assays
- Step 4: Characterize variants via in vivo critical-path assays
- Step 5: Rapidly share data readouts with the scientific community

The TRACE WG has launched five subgroups to investigate prioritized topics related to the investigation of emerging variants: (1) Deep Sequencing Analysis Subgroup, (2) Reference Material Subgroup, (3) Emerging Variant Prioritization Subgroup, (4) Critical Assays Subgroup, and (5) Industry Data Sharing Subgroup. The TRACE WG, as well as its five subgroups, has representation from academia, government, industry, and nonprofits.

Discussion

Dr. Sigal recommended integrating the TRACE WG effort with international surveillance efforts because variants of interest will emerge globally. Dr. Corey agreed with this recommendation and noted that there are efforts underway.

Next Steps

Individuals interested in participating in the TRACE WG should reach out to Dr. Menetski ((b) (6) or Dr. Santos ((b) (6) The next Vaccines WG meeting will discuss considerations for the development and introduction of second-generation vaccines.

Appendix A: Participants List

WORKING GROUP MEMBERS

Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI), National Institutes of Health (NIH)*

Paula Annunziato, MD, *Vice President, Vaccine Clinical Development, Merck*

Ann Arvin, MD, *Professor of Pediatrics and Microbiology & Immunology, Stanford University*

Susan Buchbinder, MD, *Director of Bridge HIV, San Francisco Department of Public Health, and Professor, UCSF*

Larry Corey, MD, *Professor and Principal Investigator, University of Washington and HIV Vaccine Trials Network, and Past President and Director, Fred Hutchinson Cancer Research Center*

Peter Hotez, MD, PhD, *Dean for the National School of Tropical Medicine, Baylor College of Medicine, and Director, Texas Children's Center for Vaccine Development*

Antonio Lanzavecchia, MD, *Director, Immune Regulation, Institute for Research in Biomedicine*

Peter Marks, MD, PhD, *Director, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA)*

John Mascola*, MD*, *Director, Vaccine Research Center, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Paul Offit, MD, *Professor, University of Pennsylvania, and Director, Vaccine Education Center, Children's Hospital of Philadelphia*

Michael Santos, PhD, *Associate Vice President, Science, Foundation for the NIH (FNIH)*

Hanneke Schuitemaker, PhD, *Global Health, Viral Vaccine Discovery and Translational Medicine, Johnson & Johnson's Janssen Vaccines*

Brett Tolman, MA, *Strategy Manager, Deloitte*

INVITED PARTICIPANTS

Myron Cohen, MD, *Director for Global Health & Infectious Diseases, University of North Carolina (UNC) School of Medicine*

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH*

Alan Embry, PhD, *Chief, Respiratory Diseases Branch, NIAID*

Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, NIAID, NIH*

Clint Florence, PhD, *Program Officer, Research Resource Section, OBRR, DMID, NIAID, NIH*

Ellen Gadbois, PhD, *Program Lead, Biosafety, Biosecurity, and Emerging Biotechnology Policy Division, Office of Science Policy, NIH*

Antonio Gonzalez-Lopez, MD, *Global Clinical Head, COVID-19 Vaccine US Program, AstraZeneca*

Holli Hamilton, MD, MPH, *Senior Medical Officer, BARDA*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis*

Randall Hyer, MD, PhD, *Senior Vice President, Global Medical Affairs, Moderna, Inc.*

Nicole Kallewaard, *Microbial Sciences, BioPharmaceuticals R&D, AstraZeneca*
Joanne Lumsden, PhD, *Senior Scientific Program Manager, Drug Development Partnership Programs, NCATS, NIH*
Mary Marovich, MD, *Director, Vaccine Research Program, NIAID, NIH*
Jacqueline Miller, MD, *Senior Vice President, Therapeutic Area Head, Infectious Disease, Moderna, Inc.*
Penny Moore, PhD, *Senior Scientist and Wellcome Trust Fellow in Public Health and Tropical Medicine, National Institute of Communicable Diseases*
Ashley Parker, PhD, *Health Science Policy Analyst, NIH*
Vivek Schinde, MD, MPH, *Vice President, Vaccine Clinical Development, Novavax*
Alex Sigal, PhD, *Group Leader and Assistant Investigator, Max Planck Institute for Infection Biology*
Gale Smith, PhD, *Vice President of Vaccine Development, Novavax*
Mark Sotir, PhD, *Epidemiologist, CDC*
Jenny Svarovskaia, PhD, *Senior Director, Clinical Virology, Gilead Sciences*
Natalie Thornburg, PhD, *Lead Microbiologist, Respiratory Viruses Branch, CDC*
Kanny Wan, PhD, *Research Scientist, NCATS*
Roland Zahn, PhD, *Senior Scientific Director, Preclinical Immunology, Viral Vaccines, Janssen*

FNIH STAFF
Stacey Adam, PhD, *Director, Cancer, FNIH*
Stephanie James, PhD, *Senior VP of Science, FNIH*
Joseph Menetski, PhD, *Associate VP of Research Partnerships, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

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ACTIV Daily Update - COVID-19 PPP

13 November 2020

Updates from ongoing discussions with TransCelerate:

Follow up on key takeaways from 10/22 meeting:

Action Item #1

(b)(4) has developed an (b)(4).

(b)(4), (b)(6)) provided an update on 10/27:

- (b)(4) companies have volunteered to work with the ACTIV teams to mine the (b)(4).
    - (b)(4) will take the lead with (b)(4) as a back-up if needed.
- FNIH/OWS has put together a specific request as to what kind of information we'd be looking to get from the Registry. ***Call with (b)(4) reps + OWS + FNIH teams being scheduled for 11/16 or 11/20.***

Action Item #2

(b)(4) has a good relationship with the Society for Clinical Research Sites, a kind of trade organization for clinical trial sites that takes a business-oriented approach to clinical research.

- The Society represents approximately 9500 sites in 47 countries..

(b)(4), (b)(6) has spoken further with SCRS leadership and they are keen to help. (b)(4), (b)(6). The ACTIV team will put together a specific request (types of sites, type of therapeutic experience required, the geographic spread, etc.), potentially in the form of a document that can be circulated by SCRS to an 'enriched' sub-set of their member sites that allows those sites to contact ACTIV to express interest for participation.

Call with (b)(4), (b)(6) held on 11/4. SCRS does not do proactive matchmaking but will put the ACTIV trials on its Trial Opportunity Platform and direct interested sites (U.S & international) to follow up with FNIH directly. ***Follow-up call scheduled with SCRS/OWS/FNIH for 11/13 to confirm specific inputs.***

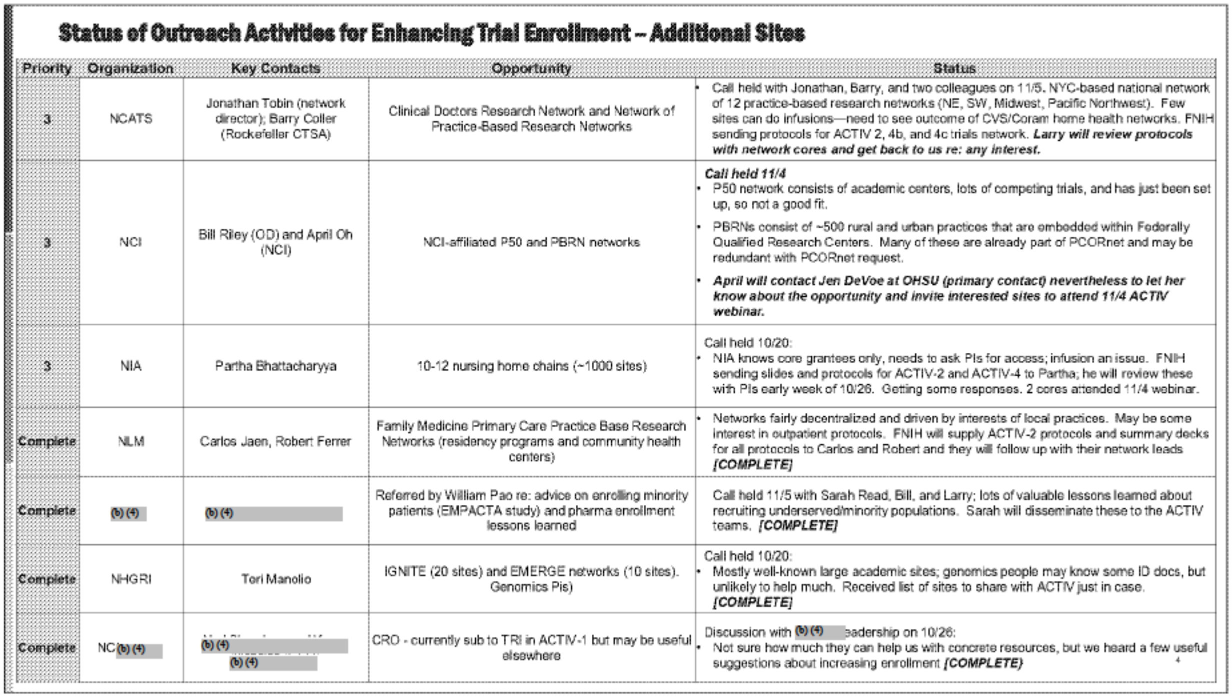
Action Item #3

Discussed the need for personnel to help all ACTIV trial teams provide administrative and logistical support to the ACTIV sites, which will be particularly critical if we hope to readily add new community-based sites in view of our existing CROs' limited bandwidth.

- **Call held with CRO Forum and (b)(4) on 11/3**. Senior leadership from 6 CROs participated (IQVIA, PPD, Covance, Icon, Parexel, and Syneos). FNIH/ACTIV requested 30-40 FTEs to help with site setup and activation.
- (b)(4), (b)(6)) has come back with interest and specific questions from several of the CROs (project/trial scope and contracting). FNIH is preparing one-pagers on each trial. ACTIV team will use feedback to create a common RFP that each CRO can bid against seperately. ***ACTIV Q&A response document created and follow-up with CRO Forum/ACRO/OWS trial reps is scheduled for 11/13.***

Status of Outreach Activities for Enhancing Trial Enrollment – Additional Sites

Priority	Organization	Key Contacts	Opportunity	Status
1	NIMH	(b) (4)	(b) (4)); 8 HMOs. Currently running suicide prevention intervention study	- *Discussion 10/27 with (b) (4)), who runs NIMH/FDA-sponsored Mental Health Research Network across several (b) (4), Henry Ford, and Partners: - Most interest will be in outpatient trials, and perhaps antithrombotics. (b) (4) very decentralized but (b) (4) follow up interest in ACTIV with (b) (4) (b) [redacted] [redacted] and with (b) s new COVID-19 czar. DW has followed up with Janet Woodcock. ***Meeting with (b) (4) [redacted] [redacted] (national contact for COVID-2 trial operations) is scheduled 11/16.***
1	NCI	Ned Sharpless and Jim Doroshow	NCTN network: 45 NCORP cores (=~500 community sites) + selected LAPS academic hubs (= 70 major cancer centers)	- Site lists have been exchanged and letter from Ned S. is finished and ready to be distributed by NIAID to selected NCI sites. PPD completed the cross-walk of existing ACTIV-2 sites against the NCI LAPS and NCORP site list. There were a total of 38 sites which did not overlap with existing ACTIV-2 sites currently under evaluation or activated; ***these will be contacted by PPD. Checking with trial teams on whether any sites have expressed interest***.
1	PCORnet	Nakela Cook, Josie Briggs, Mike Lauer	TBD - have tended to focus on post-marketing studies	- Maria Freire and David Wholley spoke with Josie Briggs on 10/26. 9 clinical hubs, over 60 organizations. Interest in outpatient and antithrombotics. Josie will approach her clinical hubs about joining ACTIV-2. Josie will approach Amy Patterson about ACTIV-4. Sites are very willing to help; have exchanges site lists. ***Still waiting to hear back from Josie.***
2	(b) (4)	(b) (4) [redacted]	***TBD – Initial call will frame how Advent Health can be helpful in accelerating our COVID-19 clinical trials***	- ***Contacts offered by Deloitte, vetted with Janet Woodcock. Call being scheduled***
2	(b) (4) *t*	(b) (4)	***TBD – Initial call will frame how Caremount can be helpful in accelerating our COVID-19 clinical trials***	- ***Contacts offered by Deloitte, vetted with Janet Woodcock. Call being scheduled***
2	NIGMS	Jon Lorsch and Ming Lei	IdEA Centers: 12 primary academic cores with affiliated community clinics	*Updates from call on 10/28: - IDeA is a Congressionally-funded program that supports clinical research in underserved areas of the country: Clinical Translational Research Centers (CTRs) which have links into practice-based networks. There is likely interest in gaining the organization and network resources that participation in national master protocols could provide. - FNIH has sent the summaries and protocols for ACTIV-1, -2,-3, -4a and -4b, to Jon and Ming which they will use to drive interest with the CTRs. FNIH has also shared IDeA slides and links with ACTIV teams. Several sites attended 11/4 webinar. CTRs in West Virginia, Hawaii, and Puerto Rico have contacted to express interest; ***more expected.***



Status of Outreach Activities for Enhancing Trial Enrollment – Additional Sites

Priority	Organization	Key Contacts	Opportunity	Status
3	NCATS	Jonathan Tobin (network director); Barry Coller (Rockefeller CTSA)	Clinical Doctors Research Network and Network of Practice-Based Research Networks	• Call held with Jonathan, Barry, and two colleagues on 11/5. NYC-based national network of 12 practice-based research networks (NE, SW, Midwest, Pacific Northwest). Few sites can do infusions—need to see outcome of CVS/Coram home health networks. FNIH sending protocols for ACTIV 2, 4b, and 4c trials network. ***Larry will review protocols with network cores and get back to us re: any interest.***
3	NCI	Bill Riley (OD) and April Oh (NCI)	NCI-affiliated P50 and PBRN networks	***Call held 11/4*** • P50 network consists of academic centers, lots of competing trials, and has just been set up, so not a good fit. • PBRNs consist of ~500 rural and urban practices that are embedded within Federally Qualified Research Centers. Many of these are already part of PCORnet and may be redundant with PCORnet request. • ***April will contact Jen DeVoe at OHSU (primary contact) nevertheless to let her know about the opportunity and invite interested sites to attend 11/4 ACTIV webinar.***
3	NIA	Partha Bhattacharyya	10-12 nursing home chains (~1000 sites)	Call held 10/20: • NIA knows core grantees only, needs to ask PIs for access; infusion an issue. FNIH sending slides and protocols for ACTIV-2 and ACTIV-4 to Partha; he will review these with PIs early week of 10/26. Getting some responses. 2 cores attended 11/4 webinar.
Complete	NLM	Carlos Jaen, Robert Ferrer	Family Medicine Primary Care Practice Base Research Networks (residency programs and community health centers)	• Networks fairly decentralized and driven by interests of local practices. May be some interest in outpatient protocols. FNIH will supply ACTIV-2 protocols and summary decks for all protocols to Carlos and Robert and they will follow up with their network leads ***[COMPLETE]***
Complete	(b) (4)	(b) (4)	Referred by William Pao re: advice on enrolling minority patients (EMPACTA study) and pharma enrollment lessons learned	Call held 11/5 with Sarah Read, Bill, and Larry; lots of valuable lessons learned about recruiting underserved/minority populations. Sarah will disseminate these to the ACTIV teams. ***[COMPLETE]***
Complete	NHGRI	Tori Manolio	IGNITE (20 sites) and EMERGE networks (10 sites). Genomics Pis)	Call held 10/20: • Mostly well-known large academic sites; genomics people may know some ID docs, but unlikely to help much. Received list of sites to share with ACTIV just in case. ***[COMPLETE]***
Complete	NC(b) (4)	(b) (4) (b) (4)	CRO - currently sub to TRI in ACTIV-1 but may be useful elsewhere	Discussion with (b) (4) eadership on 10/26: • Not sure how much they can help us with concrete resources, but we heard a few useful suggestions about increasing enrollment ***[COMPLETE]***

ACTIV Working Group Updates

PRECLINICAL

- In response to concerns from leadership about whether mink-derived SARS-CoV2 variants could enable immunologic escape from vaccines and therapeutics in development, the Preclinical WG met on Wednesday and recommended forming a small working group to provide recommendations:
    - Initial members (likely to add more) include Tomas Cihlar (Gilead), Erica Ollmann-Saphire (La Jolla Inst), Ralph Baric (UNC), Mike Diamond (Wash U, St L), Kara Carter (Evotec), Jim Anderson (OD), Christine Colvis (NCATS) and John Young (Roche)
    - The group will advise on how to best leverage ACTIV to translate changes in viral sequence to medical decisions, existing efforts around sequence tracking, high-throughput screening methods for efficacy, etc.
    - The WG made specific suggestions for members of the subgroup and identified several initial issues to be discussed at future meetings. The group will gather additional information on these as well as identify other gaps and barriers to rapid progress
    - The Preclinical management team has been meeting with individuals to gather initial recommendations:
        - Tomas Cihlar (Gilead)
            - It was highlighted that most sponsors are actively tracking changes in the viral genome at sites that are relevant to the activity of their drug
            - This could be an opportunity to create a central repository of sequencing data, structural data for viral targets & drug-target interfaces, the influence of allosteric mutations, etc.
        - Erica Ollmann Saphire (La Jolla Inst, CoVIC)
            - Described the ongoing efforts of CoVIC – performing epitope mapping, escape propensity for all major mAbs (251 total) except (b) (4) and integral molecular
            - The antibody database is blinded, but information might be able to be unblinded to allow analysis. The team will explore this possibility
    - **An initial meeting of the whole group is being set for the end of next week or early Thanksgiving week**

PRECLINICAL CONTINUED

- Preclinical Agent Prioritization Set 6 materials were distributed on 11/11:
    - 12 agents total: 5 immunomodulators, 4 antivirals, 2 symptomatic/supportive, 1 other
    - Agents will be discussed live on 11/20 to determine advancement status
- Facilitated Preclinical full WG meeting
    - Presented a preclinical prioritization scoring category to the group called "value proposition"
        - It was noticed that compounds receiving high scores are not necessarily met with enthusiasm for matchmaking or follow-up work
        - To address this concern, we created several new fields that seek to gauge the broader value of a compound relative to others, regardless of the completeness of the data package
    - We will be working with the WG members to identify additional POCs at the BSL facilities who have yet to fill out the REDCap survey as requested
- Reviewed the Small Animal Model Field Guide final draft with the co-chairs prior to the scheduled "go live" on the NCATS portal early next week
- Published a set of FAQs for the Agent Prioritization effort on the FNIH ACTIV webpage
    - Includes responses to typical questions we receive from sponsors throughout the ACTIV candidate survey submission process; includes an overview of the review process, matchmaking, confidentiality agreements, and other aspects of ACTIV
    - Hopefully will reduce the communication load between the Preclinical and Clinical WGs and sponsors

ACTIV Working Group Updates

THERAPEUTICS CLINICAL

- Monday: ACTIV-3 Discussion with Klick Health
    - Received presentation from Klick on the ACTIV-2 "Rise Above COVID" PR campaign and promotion materials
    - Discussed overview of ACTIV-3 study and current recruitment goals
    - Aligned on next steps to identify ways for Klick Health to support ACTIV-3 recruitment
- Monday: ACTIV-3/GSK-Vir Standing Meeting
    - Discussed regulatory updates – amended master protocol and Appendix H2 has been submitted to FDA, info still needed for ex-US regulatory submissions
    - Reviewed timeline and logistics of GSK-Vir's proposed shelf-life extension plan
    - Aligned on need for GSK-Vir to identify individual to assist with pharmacy training
- Monday: ACTIV-3 AZ/PCI Meeting
    - Discussed details of product release and distribution, including proposed process of shipment and requirement of QP certification
    - Confirmed that separate labels are required as ACTIV-2 and ACTIV-3 studies have different sponsors; AZ agreed that separate labels are needed
- Monday: ACTIV-2/AZ Sub Study Meeting
    - Discussed AZ's ongoing Phase 1 study; AZ has dosed all 60 subjects, blinded 1-week safety data on that group and confirmed that there are no serious adverse events
    - Reviewed logistics with IM and IV – IM will take all patients, unlike IV, which plans to have stratified randomization by duration of symptoms and high or low risk
    - Aligned on next steps and timeline for finalizing appendix
- Monday: ACTIV-2/Sagent Sub-Study Meeting
    - Reviewed Sagent's ongoing Phase 2 study and latest updates
    - Discussed frequency of dosing and feasibility of a 7-day dosing regimen; additionally, aligned on the importance of clarifying timeline for QID dosing
    - Aligned on next steps: ACTIV-2 Team to work on appendix and both groups will begin recurring bi-weekly meetings

THERAPEUTICS CLINICAL

- Monday: ACTIV-1 Operations Meeting
    - Discussed recent assessment of ACTIV-1 lab tests, completion of operational assessment for co-enrollment with ACTIV-4, and targeting completion of the protocol by 11/20
    - Reviewed enrollment and site activation numbers – 7 sites activated and planning to activate 8 sites by 11/13, with 46 US sites selected and 15 sites in Latin America
- Tuesday: Needs Assessment: Next Steps for VA Site Activation
    - Reviewed next steps for prospective assessment of VA site activation, including connecting with Laura, Libby and Rachel for inputs
    - Discussed accessing available metrics through INSIGHT
- **Tuesday:** (b) (4) [redacted]
- Tuesday: Facilitated Master Protocol Manuscript Sub Team Meeting
    - Reviewed section assignments and proposed word counts for each section
    - Aligned on next steps of uploading relevant files to Basecamp, consolidating figures, and targeting first draft by Monday 11/16
- Tuesday: Facilitated Preclinical and Clinical WG Compound Survey Review Meeting
    - Reviewed recent agent submissions for the Clinical and Preclinical WGs
- Tuesday: Facilitated Cross ACTIV Ops Internal Planning Meeting
    - Aligned on agenda for Cross Trial Operations Meeting on 11/12 –ACTIV trial status update, HHS portal update, communications contract, updated communications process, site identification efforts, and ACTIV trial data sharing
- Wednesday: Meeting with New AZ Study Coordinator for Trial Debriefing
- Wednesday: ACTIV-3 Site Investigators Meeting
    - Received update on submission of preliminary report
    - Discussed status of approval for version 2.0 of the protocol and readiness for drug distribution and training sessions once approvals are achieved
    - Reviewed focus areas for data capture and key lessons learned
    - Discussed novelty aspects of the two new drugs

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ACTIV Working Group Updates

PRECLINICAL

- Wednesday: **ACTIV-2/TOC/Lilly Meeting to Discuss EUA**
  - **Discussed implications of (b) EUA and ACTIV-2's plan to finish Phase 2 with the 700mg dose by 11/16 –** (b) (4)
- Wednesday: Brii Bio / ACTIV-2 Standing Meeting
  - Reviewed timeline for appendix review; comments on appendix will be addressed on 11/13 and sent for concurrent MO and regulatory signoffs afterwards
  - (b) (4)
- Thursday: Facilitated Cross Trial Operations Strategy & Problem-Solving Meeting
  - Received updates on ACTIV-1 through 5 – key updates include ACTIV-2 entering Phase 3 as an open label study with no placebo
  - Discussed HHS Portal timeline, targeting launch late next week
  - Reviewed communication contracts that are being secured by OWS, and aligned on cross-trial communications process
  - Discussed site identification efforts and approach to ACTIV trial data sharing
- Thursday: ACTIV-2 (b) (4)
  - Reviewed frequency of visits for patients and aligned on need for supervising the first three doses
- Thursday: Cross-Clinical Priorities & Support Model with OWS and BCG
  - Discussed plans moving forward for cross trial support and dividing the work between OWS staff, BCG, FNIH, and Deloitte

THERAPEUTICS CLINICAL

- Thursday: ACTIV-3 (b) (4)
- Thursday: Facilitated Therapeutics-Clinical Working Group Meeting
  - Received Master Protocol updates – key updates include changes to the ACTIV-2 protocol and recent ACTIV-3 submission of preliminary report to NEJM
  - Discussed recent agent prioritization efforts and upcoming evaluations of antiviral and immune modulator agents
  - Provided update on manuscript drafting efforts – targeting first drafts by 11/23
- Thursday: Meeting with John Kirwan / Pennington, LA CTR Clinical Network
  - Discussed needs, recruitment and potential support for ACTIV trials with John Kirwan, Executive Director of LSU's Pennington Biomedical Research Center in Baton Rouge
  - Reviewed site capabilities of Pennington and logistics with implementing ACTIV trials
- Thursday: Facilitated ACTIV Immune Modulator Adjudication Meeting
  - Reviewed two new immune modulator agents and re-evaluated one agent
- Thursday: Facilitated Agent Prioritization Manuscript Sub Team Meeting
  - Reviewed initial draft of language, specifically focused on Wave 1 process section
  - Decided to target next Wednesday 11/18 for updated version of the draft
- Thursday: ACTIV-2 Site Investigators Meeting
  - Discussed Covance kit shipping
  - Discussed plans for (b) agent post EUA – open label study
  - Discussed onboarding plans for Brii Bio agent

Upcoming ACTIV Working Group Meetings

Date	Time	Meeting Title
Friday November 13	9:00AM – 10:00AM EDT	Brii Bio/ACTIV-3 Sub Study Meeting
	9:00AM – 10:00AM EDT	Standing Cross Trial ACTIV Stats Meeting
	10:00AM – 11:00AM EDT	(b) (4) Sub Study Meeting
	2:00PM – 3:00PM EDT	ACTIV Antivirals Adjudication Meeting
	3:00PM – 4:00PM EDT	ACTIV Cross Trial Communications Meeting
	3:00PM – 4:00PM EDT	ACTIV (b) (4) Sub-Study Design Meeting
	4:30PM – 5:00PM EDT	ACTIV Cross Trial Ops Debrief
Sunday November 15	10:00AM – 11:00AM EDT	ACTIV 2/3 Agent Selection Committee Meeting

High-Level Meeting Summary

The Executive Committee (EC) of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Partnership met with Co-Chairs of the Preclinical and Therapeutics-Clinical (TX-Clinical) Working Groups (WGs) to review the status of EC action items from previous meetings; hear updates on the activities of both currently active WGs (i.e., the Clinical Trial Capacity WG has terminated operations and the Vaccines WG is on hold); and discuss designating clinical trials that are loosely connected to ACTIV under the new category of "ACTIV-associated trials."

Progress on Ongoing Action Items from Previous Meetings

The EC received updates on the status of ongoing action items from previous meetings, which are summarized in the table below. Additional participant comments on specific action items are summarized beneath the table.

	Action	Owner	Date Initiated	Progress Notes
1	Consider treatment of multiorgan residual symptoms in patients who have recovered from moderate and severe disease since this may soon be an urgent area of unmet medical need	NIH	7/29 Leadership Team Meeting	*In Process – update today*
2	Gary Gibbons and Andy Plump will follow-up regarding access to natural history studies using available EHR data	Andy Plump, Gary Gibbons	7/15 Executive Committee Meeting; 7/1 Leadership Team Meeting	*In Process – update today*
3	Consider further the request to establish a potential additional ACTIV workstream to create a centralized data warehouse/cloud infrastructure for sharing clinical trials and real-world evidence data on COVID; or whether simply to partner with other initiatives in this area	Francis Collins, NIH; Michelle Culp; COVID-19 R&D Consortium	6/17 Executive Committee Meeting	*In Process – update today*

On action items 1 and 2, Dr. Gary Gibbons noted that tracking multiorgan residual symptoms in recovered COVID-19 patients dovetails with NHLBI's broader efforts to track the natural history of the disease. To pursue both goals, NHLBI's Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies (CONNECTS) platform now includes processes to integrate electronic health record (EHR) data from consenting COVID-19 patients into a common registry; these data will be collected from patients irrespective of enrollment in NHLBI trials. Dr. Gibbons also highlighted the possibility of integrating EHR data gathering procedures into ACTIV's outpatient protocols (e.g., ACTIV-2) to gather early-stage natural history data on COVID-19. Dr. Janet Woodcock noted that she and her colleagues at FDA have been tracking natural history of COVID-19 in pre-hospitalized and convalescent patients and will keep Dr. Gibbons informed of those efforts.

On action item 3, Dr. (b)(6) [redacted] reported progress in (b)(4) [redacted]. He noted that (b)(4) [redacted] (e.g., (b)(4) [redacted]. Dr. Collins also noted that this topic can be removed from the list of ongoing action items because the conversations about these issues will inevitably continue.

Preclinical WG Updates

The WG has submitted its proposed combination therapy testing strategy to Operation Warp Speed (OWS), and has begun to identify which pieces of information to capture from nonhuman primate (NHP) studies to facilitate comparisons of studies conducted across the National Primate Research Centers (NPRCs).

The WG has also submitted both its Pandemic Response Drug Development SOP and its Animal Model manuscripts to *Cell Host & Microbe* for publication. The first manuscript was written for investigators who want to assist in efforts against the pandemic but who lack the translational science expertise to know what data are needed on an agent of a given class before it can enter the clinic, and is designed to help inform the diverse efforts of investigators seeking to redirect their research efforts toward helping to address COVID-19. The second manuscript documents what is known about various in vivo models in relation to COVID-19 vaccines and therapeutics development—including these models' limitations. However, the authors or this manuscript also acknowledge that knowledge about the models and about SARS-CoV-2 are in flux, and the manuscript directs readers to the NCATS OpenData Portal for the most up-to-date information.

The OpenData Portal contains the Preclinical WG's detailed descriptions of COVID-19 NHP and small animal models, which are regularly updated. The model descriptions landing page, which can be reached at https://opendata.ncats.nih.gov/covid19/animal, contains high-level animal model descriptions. Some model names form hyperlinks that users can select to view detailed descriptions, which the Preclinical WG is currently working to complete. The detailed descriptions contain information such as virus strain, disease manifestations, and comorbidities (including age), and identifies vendors that can provide the animals. Links are also provided to studies that use the model in question.

However, although NHP studies are being conducted largely within NPRCs using common master protocols, coordinating across the various small animal model studies is far more difficult. Therefore, the Preclinical WG is now developing its small animal model field guide to help standardize small animal model research in COVID-19.

The WG is also currently piloting its envisioned "matchmaking" process by which it will connect agent sponsors in need of further preclinical data with laboratories that have desired expertise and resources to help generate those data; these data will in turn facilitate agent prioritization. The WG aims to identify what it calls "preclinical-stage agents": agents that have not undergone a multiple ascending dose or any further clinical study, but that are closest to clinical trial readiness. The WG informs sponsors of data gaps identified by reviewers within ACTIV and then, jointly with NIAID, pairs those sponsors with appropriate laboratories that can generate further data to fill those gaps if the sponsor is interested.

Discussion

Dr. Mikael Dolsten suggested that the Preclinical WG, in its animal model field guide, encourage investigators to exercise caution in extrapolating animal immune responses to those in humans.

Therapeutics-Clinical WG Update

TX-Clinical WG Co-Chairs presented updates on the WG's master protocol development and agent prioritization efforts.

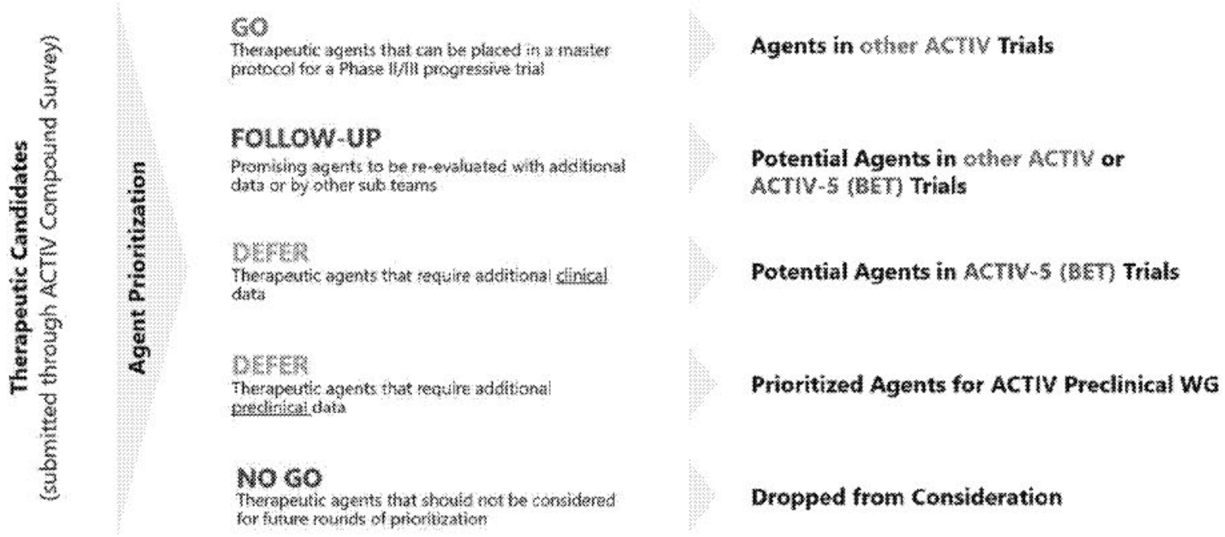
Master Protocol Development

The Master Protocol Subgroup (MPSG) has completed development of ACTIV-1, ACTIV-2, ACTIV-3, and ACTIV-4, all of which are either undergoing or have completed FDA review (via either Pre-IND or IND applications). It has also established governance bodies for its master protocols and transitioned main protocol operations to NIH and OWS. Its next steps are to coordinate with the lead networks, agencies, company partners, and CROs for each protocol to plan and execute protocol implementation.

Summary information on the status of each of the MPSG's master protocols is below:

- **ACTIV-1:** (phase III; immunomodulators; inpatients; received second round of pre-IND feedback; CRO selected and BARDA contracting in process; projected launch in late August/early September)
  - Sponsor: Duke Clinical Research Institute (DCRI) + NCATS Trial Innovation Network (TIN) + CRO
  - First agents tested will be: abatacept, cenicriviroc, infliximab
- **ACTIV-2:** (phase II/III; neutralizing monoclonal antibodies [mAbs] and oral antivirals; outpatients; trial launched on August 3; 5 sites open, first patient in soon; launched community outreach campaign to encourage patient enrollment in outpatient trial; onboarding new agents)
  - Sponsor: NIAID AIDS Clinical Trials Group (ACTG) + CRO
  - First agents tested will be: neutralizing mAbs (first (b) (4) [redacted]
- **ACTIV-3:** (phase II/III; neutralizing mAbs; inpatients; trial launched on August 4; 6 sites open, (b) (4) [redacted]; onboarding new agents; rate-limiting factor is supply of (b) (4) [redacted]
  - Sponsor: NIAID INSIGHT + NHLBI PETAL + NHLBI CTSN + VA + CRO
  - ACTIV-3 will include phase I testing option for agents that need it
  - First agents tested will be: neutralizing mAbs (first (b) (4) [redacted])
- **ACTIV-4:** (phase III; anticoagulants; inpatients; completed DSMB and central IRB review; hospitalized and pre-hospitalized cohorts projected to activate week of August 24, post-hospitalized cohort first week of September)
  - Sponsor: NHLBI-NINDS "Network of Networks"
  - Agents to be tested: 2 anticoagulants, anticoagulant + anti-platelet/thrombotics

In addition to the protocols above, the TX-Clinical WG has long discussed launching a potential **ACTIV-5** master protocol that could be designed to fill gaps not addressed by ACTIV-1/-2/-3/-4. During Wave 2 agent prioritization, the WG has identified the NIAID Big Effect Trial (BET) as a version of this protocol. Wave 2 has considered agents whose mechanisms of action (MOAs) or scientific rationales seem promising, but which lack adequate clinical data to support immediate entry into larger Phase III clinical trials. BET, which will be an inpatient Phase II proof-of-concept study designed to identify large clinical effect sizes, may test these agents. The BET master protocol will test selected agents in arms of 100 patients; each arm will be compared to a shared control arm also containing 100 patients. The Phase II clinical information generated by this trial will help inform prioritization of agents for other trials such as ACTT and ACTIV. The BET protocol was submitted to FDA the week of August 10 and is projected to launch the week of August 31. The first agents to be tested are risankizumab and lenzilumab. The graphic below shows the categories that agents evaluated for BET/ACTIV-5 can be slotted into:


Therapeutic Candidates
(submitted through ACTIV Compound Survey)
Agent Prioritization
GO
Therapeutic agents that can be placed in a master protocol for a Phase II/III progressive trial
Agents in other ACTIV Trials
FOLLOW-UP
Promising agents to be re-evaluated with additional data or by other sub teams
Potential Agents in other ACTIV or ACTIV-5 (BET) Trials
DEFER
Therapeutic agents that require additional clinical data
Potential Agents in ACTIV-5 (BET) Trials
DEFER
Therapeutic agents that require additional preclinical data
Prioritized Agents for ACTIV Preclinical WG
NO GO
Therapeutic agents that should not be considered for future rounds of prioritization
Dropped from Consideration

Agent Prioritization

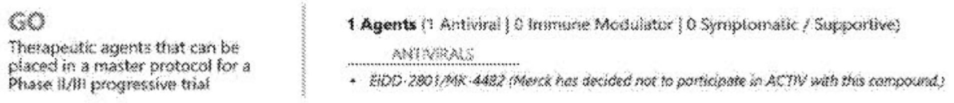
The Agent Prioritization Subgroup (APSG) continues to evaluate neutralizing Abs, antivirals, immune modulators, and symptomatic/supportive therapies for entry into ACTIV trials. It has completed Wave 2 agent prioritization of the latter three agent classes and has endorsed five neutralizing Abs for entry into ACTIV-2/-3.

Neutralizing mAbs

The ACTIV-2/-3 Agent Selection Committee (ASC) has evaluated 10 neutralizing monoclonal antibodies (mAbs), and the Trial Oversight Committee (TOC) has approved five of these (i.e., from (b) (4) [redacted]) to advance for clinical trial planning by the ACTIV-2/3 teams; these approvals are contingent on positive readouts from Phase I testing. Several other neutralizing Abs have been deferred pending additional data (from Molecular Partners, (b) (4) (b) (4) (b) (4) [redacted] Because some incoming Abs will require approval by FDA's Center for Biologic Evaluation and Research (CBER) rather than by its Center for Drug Evaluation and Research (CDER), APSG members are engaging with FDA to prepare a streamlined CBER regulatory pathway.

Wave 2 Agent Prioritization

In collaboration with the Preclinical WG, the APSG Subteams for prioritizing Antivirals, Immune Modulators, and Symptomatic/Supportive Therapies have completed Wave 2 prioritization, the results of which are shown in the table below. Wave 3 agent prioritization will begin soon:



GO Therapeutic agents that can be placed in a master protocol for a Phase II/III progressive trial	**1 Agents** (1 Antiviral | 0 Immune Modulator | 0 Symptomatic / Supportive) ANTIVIRALS - *EIDD-2801/MK-4482 (Merck has decided not to participate in ACTIV with this compound.)*

(b) (4) [redacted]

Discussion

Drs. Eric Hughes and William Pao agreed on the importance of sharing failed trial data to avoid wasting resources testing agents known to be ineffective. Dr. Sarah Read also confirmed for Dr. Collins that ACTIV and NIAID are actively communicating with international researchers (including those in the United Kingdom) through the World Health Organization (WHO) and other institutions.

Dr. (b)(4), (b)(6) [redacted] noted that the (b)(4) [redacted], and asked Drs. Hughes and Read how the APSG might identify better antiviral candidates. Drs. Hughes and Read explained that the WG was limited by the decision to assess only agents submitted via the Compound Survey, but also noted that the WG has selected only antivirals that are not already being adequately tested by other groups, and that current preclinical testing of antiviral agents will likely enhance the quality of candidates for future waves of agent prioritization. Dr. Dolsten suggested that the WG more proactively solicit antiviral candidate submissions and highlighted the advantage of antivirals (e.g., over Abs) because they often exhibit cross reactivity across various coronaviruses, particularly if they target polymerases or proteases.

Discussion: Designation of "ACTIV-Associated Trials"

Dr. Collins suggested that clinical trials that are connected to ACTIV but that have not been designed by ACTIV WGs (e.g., the INSIGHT 013 hyperimmune intravenous immunoglobulin [hIVIG] trial) be designated under a new, carefully curated category of "ACTIV-associated trials."

The EC generally endorsed this idea, and FNIH will communicate it to ACTIV's Leadership Team.

Discussion

In discussing the (b)(4) [redacted] trials, participants acknowledged that (b)(5) [redacted]. Dr. (b)(6) [redacted] also noted that (b)(5) [redacted]

Participants also discussed (b)(5) [redacted] Dr. (b)(6) [redacted] noted (b)(5) [redacted] However, Dr. (b)(6) [redacted] reassured (b)(5) [redacted].

Adjourn

A full ACTIV Leadership Team meeting will occur on Wednesday, August 26 at 3:00-4:00pm ET.

Appendix A: Participants List

Francis Collins, MD, PhD, *Director, National Institutes of Health (NIH) (Session Leader; Executive Committee Co-Chair)*
Paul Stoffels, MD, *Vice Chairman of the Executive Committee and Chief Scientific Officer, Johnson & Johnson (Executive Committee Co-Chair)*
James Anderson, MD, PhD, *Senior Investigator, National Heart, Lung, and Blood Institute (NHLBI)*
Christopher P. Austin, MD, *Director, NCATS, NIH*
John T. Burklow, *Associate Director for Communications and Public Liaison, NIH*
Christine Colvis, PhD, *Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH*
Michelle Culp, MPH, *Office of the Director, NIH*
Gary Disbrow, PhD, *Acting Director, Biomedical Advanced Research and Development Authority (BARDA)*
Mikael Dolsten, MD, PhD, *CSO and President, Worldwide R & D, Pfizer*
Maria Freire, PhD, *President and Executive Director, FNIH*
Ellen Gadbois, PhD, *Office of Science Policy, Office of the Director, NIH*
Gary H. Gibbons, MD, *Director, NHLBI, NIH*
Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis*
H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID*
Peter Marks, PhD, *Director, Center for Biologics Evaluation and Research, FDA*
William Pao, PhD, MD, *Head, Pharma Research & Early Development, Roche/Genentech*
Ashley Parker, PhD, *Health Science Policy Analyst, NIH*
Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH*
Lawrence Tabak, DDS, PhD, *Principal Deputy Director, NIH*
Janet Woodcock, MD, *Director, Center for Drug Evaluation and Research (CDER), FDA*
John Young, PhD, *Global Head, Infectious Diseases, Roche*

Stacey Adam, PhD, *Director, Foundation for the NIH (FNIH)*
Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*
Karen Tountas, PhD, *Scientific Program Manager, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Rosa Maria Alvarez, *Manager, Deloitte*
Margaret Anderson, *Managing Director, Deloitte*
Helen Q. Chen, PhD, *Manager, Deloitte*
Olivia Elsaid, *Consultant, Deloitte*
Nina Gonzalez, *Senior Manager, Deloitte*
Harrison Hawk, *Consultant, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc*

High-Level Meeting Summary

The ACTIV Agent Prioritization Subgroup's Immune Modulators (IMs) Subteam reviewed scores for eight IMs for inclusion in ACTIV trials. Two agents were identified for immediate follow-up, five were deferred, and one was transferred to the Symptomatic/Supportive Therapies Subteam. The Subteam also refined the possible outcomes of the initial round of scoring to emphasize that scoring should act as the first stage in group discussion and debate.

Immune Modulators

(b) (4)

Scores for (b) (4) and another weak. Dr. (b) (6) emphasized that studies of (b) (4) , but studies of the drug (b) (4) . However, Dr. (b) (6) noted that Dr. (b) (6) who was not present at the meeting) saw greater promise in (b) (4) . Subteam members agreed that (b) (4) should be assessed by three additional reviewers to resolve this discrepancy.

Dr. (b) (6) suggested that (b) (4) , which has been observed in severe cases of COVID-19, would be more promising than (b) (4) he suggested the Subteam consider (b) (4) . Preclinical evidence suggests (b) (4) , and the Subteam may have a later opportunity to review that combination.

(b) (4)

Although (b) (4) . Drs (b) (6) explained that they (b) (4) at the time of review. Dr. (b) (6) (b) (6) noted that the (b) (4) ; Subteam members (b) (4)

Participants discussed several parameters for consideration when data become available. Dr. (b) (6) noted that recent studies have suggested (b) (4) Thus, (b) (4) . Participants also discussed its route of administration in outpatient trials. Dr. (b) (6) suggested that (b) (4) , whereas Drs. (b) (6) and (b) (6) (b) (6) saw (b) (4) .

Data on approximately (b) (4) and outpatient participants enrolled in several small trials of (b) (4) will likely be available in upcoming months. Dr. (b) (6) however, cautioned that these trials may be insufficiently powered to reveal a signal without a very large effect. The group decided to wait for maturation of the current trials before re-evaluating for inclusion in the ACTIV trials.

(b) (4)

(b) (4) ories. However, Subteam members suggested that ongoing clinical trials (b) (4) . Drs. (b) (6) and (b) (6) observed that various other (b) (4) Phase II trial (b) (4) . Moreover, Dr. (b) (6) noted that preliminary data suggests the (b) (4) . The Subteam thus decided (b) (4) s before revisiting this agent.

(b) (4)

(b) (4) . Dr. (b) (6) noted (b) (4) However, Dr. (b) (6) suggested that this (b) (4) Moreover, (b) (4) . However, Subteam members (b) (4) . ACTIV will monitor the results of ongoing trials of this agent—(b) (4) when more data become available. Dr. (b) (6) noted that it may be considered as a (b) (4) .

(b) (4)

Subteam members generally (b) (4) . Dr. (b) (6) (b) (4) and Dr. (b) (6) (b) (6) (b) (4) . Dr. (b) (6) will ask the Preclinical Working Group (WG) to advise (b) (4) run by NIAID. The Subteam will defer further (b) (4) become available.

(b) (4)

While reviewers rated the (b) (4) , Drs. (b) (6) and (b) (6) agreed (b) (4) Dr. (b) (6) will ask the Preclinical WG to advise (b) (4) run by NIAID. The Subteam will (b) (4) become available. Dr. (b) (6) b) (4)

(b) (4)

Dr. (b) (6) noted most reviewers recommended transferring (b) (4) to the Symptomatic/Supportive Therapy Subteam. The Subteam (b) (4)

(b) (4)

The Subteam discussed the importance of one no-go score for (b) (4) Dr. (b) (6) explained that a (b) (4) although the company provided a (b) (4) Dr. (b) (6) noted that an ongoing clinical trial with 1,034 symptomatic infected patients suggested the drug showed (b) (4), and Dr. (b) (6) noted that he has reviewed data showing (b) (4) The Subteam agreed to (b) (4) from the ongoing clinical trial.

Change to Initial Scoring Outcomes

Participants discussed how the scoring system can appear to give agents a misleading early imprimatur of approval. Even strong initial scores are not intended to automatically move an agent forward, but instead to provoke continued discussion and debate in order to ensure that only the most promising agents are accepted into trials. At Dr. Aggarwal's suggestion, the Subteam agreed to change scoring outcomes to reflect this expectation: the option to "keep" an agent will be eliminated, leaving only "adjudicate" and "drop" as options.

Next Steps

Dr. Adam will arrange for three additional reviews of (b) (4) t to occur before forwarding its scores to the Agent Prioritization Review Committee. She will also arrange for Subteam members to sign confidentiality agreements to gain access to further data regarding (b) (4) ACTIV will continue to track new data for deferred agents and will reconvene the Subteam when a threshold number of additional compounds become available for assessment.

Appendix A: Participants List

Subgroup Members

Neil Aggarwal, MD, *Branch Chief, Lung Biology and Disease, Division of Lung Diseases, National Heart, Lung, and Blood Institute (NHLBI), NIH*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Gregory Deye, MD, *Medical Officer/Program Officer, NIAID*

Josh Fessel, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Carl Garner, PhD, *Vice President, Global Regulatory Affairs, Eli Lilly and Company*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

James McNamara, MD, *Autoimmunity and Mucosal Immunology Branch Chief, NIAID*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Tony Punturieri, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Mark Robien, MD, *Medical Officer, NIAID*

Yves Rosenberg, MD, MPH, *Branch Chief, NHLBI*

Alkis Togias, MD, *Branch Chief, Allergy, Asthma and Airway Biology, NIAID, NIH*

Michael Vincent, MD, PhD, *Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

Peter Wung, MD, MHS, *Associate VP, Global OMD Lead, Immuno-Inflammation, Sanofi*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Rosa Maria Alvarez, PhD, *Senior Consultant, Monitor, Deloitte*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Josh Fessel (NIH/NHLBI) to Everyone: 05:13 PM

Yes, definitely.

From Stacey Adam to Everyone: 05:15 PM

Thanks, Josh!

From Timothy Buchman to Everyone: 06:00 PM

https://clinicaltrials.gov/ct2/show/NCT04393038

https://www.biospace.com/article/abivax-treats-first-patient-in-phase-2b-3-abx464-covid-19-clinical-trial/

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard status updates from its Master Protocol Subgroup (MPSG) and discussed ways ACTIV could facilitate outpatient clinical trials on approved agents with COVID-19 therapeutic promise.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5).

ACTIV-1: Immunomodulators (Inpatient Phase III)

ACTIV-1 has activated 28 sites (plus an additional 3 satellite hospital sites) and enrolled 203 participants. Thus far, the enrolled patient population has sufficient representation of African Americans and Asians, but requires more Hispanic representation. The ACTIV-1 team has selected an additional 82 U.S. sites and 22 ex-U.S. sites and received regulatory approval to begin activating sites in Argentina and Peru, with approval expected soon from Mexico and Brazil.

The trial team met with the ACTIV-1 DSMB this week and received safe-to-proceed approval for each of the three ACTIV-1 agents. The team submitted a protocol amendment to FDA, which raised concerns that co-enrollment with ACTIV-2 would inappropriately mix different patient populations and thus recommended the team perform subgroup analyses; the team does not agree with this concern, but may incorporate additional patient stratification processes to control for patient population differences. The team is now developing a response to the FDA comments.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has activated 94 sites and (b) (4) Enrollment for the (b) (4) agent will close on January 15 and has begun for the (b) (4) agent (with approximately 20 patients in the (b) (4) arm as of today). The ACTIV-2 team is working with Black-led organizations to improve patient enrollment within the Black community and is working to activate international sites in Argentina, Peru, and South Africa.

The team received safe-to-proceed approval from the FDA for Version 3.0 of the master protocol, which includes the IM- and IV-administered agents from (b) (4), the inhaled interferon agent from (b) (4), and camostat mesylate; it aims to begin enrollment for these agents soon. The team is now developing Version 4.0 of the master protocol, which will include a polyclonal antibody from SAB. The team anticipates soon sharing data from the (b) (4) arm of ACTIV-2, including virology and fully sequenced viral isolate data.

Discussion

Drs. Judy Currier and Lisa LaVange agreed to review the locations of ACTIV-1 and -2 sites in order to evaluate whether a sufficient patient population is possible for both trials.

Dr. John Mellors noted that, in addition to the ACTIV trials, many other initiatives are starting to sequence SARS-CoV-2 variants within clinical trial samples, including samples from patients treated with mAbs, convalescent plasma samples, and post-vaccination samples.

Participants discussed the ongoing and collaborative effort between Operation Warp Speed (OWS) and the Preclinical-Therapeutics WG, which aims to evaluate differences in agent potency against different virus strains and share generated data with sponsor companies. The effort is led by Drs. Ann Eakin and Karl Erlandson and has thus far generated a white paper detailing its objectives and activities. Dr. Libby Higgs recommended creating a more robust link between this effort and the TX-Clinical WG. Dr. Mellors recommended that this effort test variants at multiple labs in order to assess the great variability between viral assays. Drs Joe Menetski and Eakin will likely present on this initiative's efforts during the next TX-Clinical WG meeting.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

ACTIV-3 has activated 30 sites and (b) (4) in Version 2.0 of the master protocol, which includes the (b) (4) agents. The ACTIV-3 team aims to soon launch Version 3.0 of the protocol, which includes the AstraZeneca dual antibody agent. The team has received FDA comments on Version 3.0, one of which was a recommendation to incorporate language into the consent form to notify patients of relative uncertainty related to interactions between vaccine-derived antibodies and the agents.

The team is working to activate international sites, but has found that many countries wish to review preliminary data on the ACTIV-3 agents, particularly the Brii Bio agent, before approving site recruitment. However, the team believes activating sites for the (b) (4) and (b) (4) agent trials will be easier than for the Brii Bio agent.

The team will soon submit to the FDA Pulmonary Critical Care Division the finalized plan for the ACTIV-3B aviptadil and r(b) (4) factorial study. The ACTIV-3 DSMB recently reviewed the ACTIV-3 hyper immunoglobulin sub-study's blanket sample analyses and recommended continuing with a target sample size of 5,000 patients.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4's in-hospital protocol (4A) has activated 54 sites in the U.S. and Spain and enrolled 874 patients in collaboration with partnering networks, including the Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) and Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) Trials. Upon ACTIV-4A's recommendation, the ACTIV-4A team halted enrollment of patients requiring ICU-level care into the clinical trial. The team will soon finalize its plan to incorporate a P2Y12 inhibitor arm into ACTIV-4A and aims to begin enrolling patients into this arm after the ACTIV-4A DSMB meeting on January 20.

The ACTIV-4 pre-hospitalized protocol (4B) has activated 11 sites and enrolled 85 patients. The ACTIV-4B team aims to soon finalize an agreement with CVS to leverage MinuteClinic locations for patient enrollment.

The post-hospitalized protocol (4C) is expected to launch and begin enrolling patients soon. The ACTIV-4C team has received the first shipment of drug supply.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

ACTIV-5 has activated nine sites and (b) (4). The ACTIV-5 team has selected an additional 16 sites and aims to soon activate them. The team continues to work to increase site activation and to select additional agents for future BETs.

Potential Avenues to Test Approved Agents for Outpatients

ACTIV leadership, as well as many ACTIV WGs and Subgroups, have recently discussed the need to integrate an additional effort, or master protocol, to begin evaluating agents currently approved for other indications that have shown possible promise as a COVID-19 therapeutic. Most of these agents are immune modulators that have been studied in multiple small studies; the potential benefit of some of these agents have been publicized by these studies, causing clinicians and researchers to feel public pressure to further evaluate these agents before translating them into clinical practice against COVID-19.

Drs. Cliff Lane and Sarah Read proposed the following four approaches to test approved agents in a high-quality, large-scale clinical trial within an outpatient setting:

- (b) (4) which is initiating similar efforts and may provide helpful protocols
- Design and initiate a new master protocol, ACTIV-6, which would be a pragmatic outpatient trial that would appear similar to the (b) (4)
- Discuss partnering with a new (b) (4) evaluating similar agents
- Incorporate a sub-study into ACTIV-2 to evaluate these agents in a pragmatic outpatient trial

Each of these proposed approaches would be "low touch" (i.e., require less hands-on effort and more remote interactions) and use straightforward clinical endpoints to provide a quick and reliable answer regarding the various agents that have been proposed to be efficacious against COVID-19, particularly (b) (4).

Discussion

Participants agreed that ACTIV has the unique opportunity to provide definitive answers rigorously and quickly for many agents in relation to COVID-19 and that this opportunity should be pursued. They also agreed that creating a new protocol would require significant time and effort and thus that leveraging existing resources, such as existing protocols, would be preferred. Dr. LaVange suggested performing a cost-benefit analysis to help the TX-Clinical WG decide on a preferred approach.

Dr. Jacqueline Kirchner noted that the (b) (4) study is enrolling well and continues to incorporate more agents. She added that certain agents currently under evaluation at (b) (4)

(b) (4) may be more appropriate for ACTIV, and vice versa, and thus additional discussions between the TX-Clinical WG and (b) (4) would be helpful. Participants agreed that meeting with both the (b) (4) research group would help provide insights into a cost-benefit analysis and help formulate ACTIV's approach. Dr. Adam will contact both the (b) (4) research groups to discuss their efforts and possible synergies with a future ACTIV effort. Dr. Adam will also contact the (b) (4) to discuss the possibility of facilitating this effort through ACTIV.

Dr. Currier noted that whereas ACTIV-2 is at capacity, its established infrastructure could be leveraged to evaluate additional agents in a "low touch" approach; participants agreed with this potential approach, but also noted that further discussion is required.

Participants suggested performing a meta-analysis of the multiple small trials for a given approved agent; however, obtaining the data to perform such analyses—particularly data from negative and unpublished studies—can be difficult.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, National Heart, Lung, and Blood Institute (NHLBI)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority*

Joan Butterton, MD, *VP, Clinical Research, Infectious Diseases, Merck & Co.*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBIs*

Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*

H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID, NIH*

Lisa LaVange, PhD, *Professor and Associate Chair, Department of Biostatistics, UNC Chapel Hill*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, University of Pittsburgh*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID (WG Co-chair)*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

INVITED PARTICIPANTS

John Beigel, PhD, *Division of Microbiology and Infectious Diseases, NIAID, NIH*

Michelle Culp, MPH, *Office of the Director, NIH*

Ellen Gadbois, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*

Joanne Lumsden, PhD, *NCATS*

Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*

Hilary D. Marston, MD, MPH, *Medical Officer/Policy Advisor, NIAID, NIH*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Amanda Peppercorn, MD, *Senior Medical Director, Infectious Disease, GlaxoSmithKline (GSK)*

Martha Petrovick, *MIT Lincoln Laboratory*

Revell Phillips, PhD, *Science and Technology Manager, Defense Threat Reduction Agency*

Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*

Ronald Reisler, MD, MPH, *Senior Clinical Advisor, Davis Defense Group*

Daniel Rubin, PhD, *Statistician, Center for Drug Evaluation and Research, FDA*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*
David Wholley, MPhil, *Senior Vice President of Research Partnerships, FNIH*

Helen Chen, PhD, *Consultant, Deloitte*
Evan Appell, *Consultant, Deloitte*
Hana Nasr, MPH, *Consultant, Deloitte*
Alex Sorosa, *Business Analyst, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Libby Higgs to Everyone: 01:08 PM

Also cannot hear stacey but can hear everyone else...

From Robert Malone to Everyone: 01:09 PM

likewise

From Sarah Read to Everyone: 01:09 PM

maybe try to log off and back on? I can hear her well

From Robert Malone to Everyone: 01:09 PM

I did as recommended already

From Libby Higgs to Everyone: 01:09 PM

Yes I did, no difference!

From Neil Aggarwal to Everyone: 01:09 PM

So weird. Selective listening to Stacey :)

From Libby Higgs to Everyone: 01:10 PM

Yes, true Neil! Missing all her wisdom

From Libby Higgs to Everyone: 01:14 PM

Great work Judy.

From Stacey Adam to Everyone: 01:19 PM

The OWS is linked to the ACTIV Preclinical effort

From Stacey Adam to Everyone: 01:19 PM

Ann and Karl are helping to spearhead both

From Neil Aggarwal to Everyone: 01:25 PM

Libby, re: ACTIV3b - TESICO. I could not agree more. Great leadership on your part.

From (b) (6) to Everyone: 01:51 PM

(b) (5) [redacted]

From (b) (6) [redacted] to Everyone: 01:54 PM

What's the reference: re: (b) (5) [redacted]

From (b) (6) [redacted] to Everyone: 01:55 PM

Challenge with the (b) (5) [redacted]

From Revell Phillips to Everyone: 01:56 PM

In my mind the inclusion of all the different studies is part of the strength - in that you are looking at lots of data...

From Jacqueline Kirchner to Everyone: 01:58 PM

Stacey: I will connect you to folks at BMGF and GatesMRI to enable the clinical discussion. Very timely.

From Jacqueline Kirchner to Everyone: 01:58 PM

Happy to include each ACTIV trial lead as well if appropriate

From Stacey Adam to Everyone: 01:59 PM

Thanks, Jacqueline

From Stacey Adam to Everyone: 01:59 PM

I will follow up with you offline

From Jacqueline Kirchner to Everyone: 01:59 PM

Has ACTIV considered IFNbeta?

From Yves Rosenberg to Everyone: 01:59 PM

But can ACTIV-2 really do quickly a large pragmatic)virtual) trial?!?

From Jacqueline Kirchner to Everyone: 01:59 PM

ACTIV2?

From Libby Higgs to Everyone: 01:59 PM

(b) (4) [redacted] colleagues have shared their protocol previously.

From Stacey Adam to Everyone: 01:59 PM

Yes, ACTIV-2 is doing inhaled IFN-beta and ACTT-3 did injectable IFN-beta

From Tim Buchman to Everyone: 02:00 PM

these are tactical questions. do we want a mm

From Libby Higgs to Everyone: 02:00 PM

Agree Tim. Janet said she would work to get OWS support for such a study.

From John Mellors to Everyone: 02:01 PM

Apologies, have 2 PM call.

From Tim Buchman to Everyone: 02:01 PM

are we agreed there is a need to test these types of agents? it seems so

From Revell Phillips to Everyone: 02:01 PM

Make sure you consider the possibility of looking at combinations of agents

From (b) (6) [redacted] **to Everyone: 02:02 PM**

(b) (5) [redacted]

From Libby Higgs to Everyone: 02:02 PM

Yes, it sounds like alignment, just best way forward is uncertain.

From Tim Buchman to Everyone: 02:02 PM

thanks for leading this discussion. so important

From Neil Aggarwal to Everyone: 02:03 PM

And timing may not be on our side...

From Eric Hughes to Everyone: 02:03 PM

thank you Stacey! 👍

High-Level Meeting Summary

The Vaccines Working Group (WG) convened to discuss implications of variants of concern (VOCs) for vaccine development, with a framing presentation by Dr. Doug Lowy on how to approach vaccine modification followed by a discussion among WG members.

Viral Variant Evidence Needed to Consider Modifying Current SARS-CoV-2 Vaccines

Doug Lowy, MD, NIH

Vaccines have exhibited apparently diminished efficacy in trials in South Africa, where the 501Y.V2 variant was highly prevalent (causing at least 90% of the cases) during the trials, raising questions about what data or evidence may be needed to consider modifying the composition of current vaccines: three vaccines showed ~10-60% efficacy against symptomatic disease in South Africa, compared to ~70-90% efficacy against the same endpoint in trials in other regions. There is currently limited evidence on the efficacy of vaccines against more serious endpoints in South Africa compared to other regions.

Evidence That Could Motivate Modifying Current Vaccines

Data meeting two possible requirements could be considered to motivate modifying vaccine composition: (1) one or more current vaccines provides "insufficient efficacy" against one or more variants, and (2) the incidence or prevalence of variants with "insufficient efficacy" is increasing or predominant. These criteria require definitions of insufficient efficacy and of increasing incidence/prevalence, and they raise the question of how to handle scenarios in which some but not all vaccines meet the agreed-upon definitions.

Recommendations (b) (5) [redacted]

(b) (5) [redacted]

(b) (5) [redacted]

(b) (5) [redacted]

(b) (5) [redacted]

Discussion

Timing of Vaccine Modification

Dr. John Mascola emphasized that U.S. regulators may face decisions about vaccine modification in the near future; as long as only the 501Y.V1 / B.1.1.7 variant rises in prevalence, this decision may be less pressing [because vaccines appear to protect against it well], but increasing circulation of variants with resistance mutations would be more concerning. Dr. (b) (6) [redacted] agreed (b) (5) [redacted] e.

Dr. (b) (6) [redacted] (b) (5) [redacted] Dr. (b) (6) [redacted] (b) (5) [redacted] Dr. (b) (6) (b) (5) [redacted] th Dr. (b) (6) [redacted] (b) (5) [redacted]

Dr. (b) (6) [redacted] noted (b) (5) [redacted]. Dr. Marks clarified that FDA guidance published on February 22 requires immunogenicity studies and potentially boost studies in previously vaccinated individuals. Although immunogenicity studies are currently required for vaccines against variants, after some number of vaccines have gone through the process (and almost certainly after identification of correlates of protection), the VRBPAC may agree that non-clinical data is sufficient for approval.

Dr. Ann Arvin asked what is known from influenza about the timeline to move from selection of a viral strain to delivery of a vaccine against that strain. Dr. Marks said that the influenza timeline from strain to shipping product varies from approximately 4 months for recombinant protein vaccine to 6 months for egg-based vaccines. Dr. Marks pointed out that influenza does not require clinical testing; for COVID-19 vaccine platforms like mRNA the time to develop the new vaccine may be very short, but initially safety and immunogenicity will need to be evaluated clinically and that will be the limiting step in the timeline.

Dr. Greg Glenn asked how the FDA would approach strain selection for subsequent vaccines. Dr. Marks said that this has been discussed between the FDA and the WHO and EMA. He explained that the WHO would likely recommend strains, which would then be reviewed by VRBPAC, similar to the process for flu, speculating that a recommendation for introduction of new vaccines could be as soon as the next few months depending on data from surveillance. Dr. Marks also emphasized the value of better surveillance data in the U.S.

Dr. Kathy Neuzil noted that while strain selection is one issue, a second is whether new strains will require the development of bivalent or multivalent vaccines. Dr. Marks noted that this question is addressed in FDA guidance: a bivalent vaccine may not be required if a vaccine matched to a variant sufficiently cross-protects against the ancestral strain; if vaccines against new variants have severely reduced neutralization against the ancestral strain, then a truly bivalent vaccine may be required.

Dr. Lowy asked whether Dr. Marks would agree that decisions about introduction of new vaccines should be defined with respect to the prevalence of variants in a vaccinated rather than unvaccinated population. Dr. Marks suggested that once the majority of a population is vaccinated, this focus would be appropriate; however, at current U.S. vaccination levels (which remain far below 50%), vaccines targeted to new variants that are currently circulating may protect naïve individuals and intervene effectively in the pandemic.

Utility of Neutralizing Ab Data as Predictor of Vaccine Efficacy

Dr. Glenn noted that (b) (4) clinical trial data provide an opportunity to make a comparison across variants. (b) (4) trials in the UK and South Africa coincided with the emergence of variants: in the UK, the 501Y.V1 variant accounted for approximately 50% of the cases in the per protocol population, and in South Africa the 501Y.V2 variant accounted for more than 90% of the cases. (b) (4) vaccine efficacy varied against different variants, showing 96% efficacy against matched strains, 85% efficacy against 501Y.V1, and 60% efficacy [in HIV- participants] against 501Y.V2.

The attack rate in (b) (4) s South African placebo groups was approximately 5% across baseline seropositive and seronegative participants, suggesting that Abs from natural infections with the ancestral strain had no impact on variant case incidence. In addition, baseline seropositive participants in the vaccinated arm did not show any improved efficacy compared to vaccinated baseline seronegatives, implying that even when boosted by vaccination natural immunity from infection with an ancestral strain does not confer any protection against 501Y.V2. This suggests that herd immunity may require strain-specific immunity, though vaccines presenting homologous spike proteins do appear to provide some cross-protection. (b) (4)'s Phase III flu trial of an adjuvanted nanoparticle vaccine generated a broad immune response that retained efficacy against influenza drift, aligned with the apparent partial cross-protection seen with their COVID-19 vaccine candidate.

Dr. Peter Hotez suggested that neutralizing Ab titers may be good predictors of efficacy against variants. He noted that neutralization titers appear to correlate with vaccine efficacy, even for (b) (4). He hypothesized that a sufficiently high neutralization titer against the ancestral strain may provide a margin sufficient to preserve vaccine efficacy despite decreased neutralization against 501Y.V2. If this hypothesis is correct, the low Ab titers displayed by the Gamaleya adenovirus vaccine, CanSino adenovirus vaccine, and Sinovac inactivated virus vaccine suggest those vaccines would not protect well against 501Y.V2. Dr. Michael Santos noted that during the last Vaccines WG meeting Drs. Penny Moore and Alex Sigal presented data showing that higher neutralization against the ancestral strain predicts higher neutralization against 501Y.V2 at the individual serum level.

Dr. Mascola pointed out that neutralizing Ab titers will decrease over time, so that eventually vaccine recipients will have low titers even for vaccines that induce high initial titers. Given that infection will trigger an anamnestic immune response, it's not clear whether circulating titers will be predictive or whether clinical data on protection will be required.

Dr. Glenn agreed that current data have been generated during an ideal window when immune responses are at their peak, and the next important question for variants is how immunity will change over time. Vaccine developers should be reporting immunogenicity data at 6 to 12 months post-vaccination soon to inform the rate of waning of Ab levels. He noted that one might have expected conservation of T-cell epitopes across variants to result in natural cellular immunity raised against the ancestral strain to provide good cross-protection against disease due to 501Y.V2, but that was not observed in Novavax's South Africa trial. This suggests that Ab responses are the key correlate of protection and waning Ab levels should motivate boosting, potentially with vaccines matched to circulating variants.

Dr. Corey mentioned that recent OWS lab data showed considerably lower pseudovirus neutralization levels for the (b) (4) compared to published Phase I trial data from other labs, suggesting that the contribution of antibody responses to protection may be lower than originally expected, and raising the question of whether cellular responses are responsible for the high levels of protection against severe disease. Dr. Glenn pointed out that there is limited efficacy data to calibrate the level of neutralization that correlates with clinical protection for variants, unlike with the ancestral strain; the relationship may not be consistent across variants. For (b) (4), there does appear to be a correlation between neutralization across variants and clinical efficacy, but Dr. Glenn expressed his hesitancy to extrapolate too much from neutralization to efficacy. Dr. Santos added that Dr. Michael Diamond has suggested that assays in ACE2 overexpressing cells might skew RBD- vs NTD-focused neutralization responses, which may complicate the assessment of ancestral strain and RBD mutant variants.

Dr. Mike Cohen suggested that mAbs represent a relatively simple test of the hypothesis of the role of Ab-mediated immunity, and although mAbs would not replicate the polyclonal response of a vaccine, passive administration studies may be able to quickly provide some insight into the efficacy of Ab responses against variants. That is to some degree what is happening currently with (b) (4). Dr. Cohen suggested that there are many mAbs and that the field ought to think creatively about how they can be used to inform questions about vaccine efficacy.

Dr. Kathy Neuzil agreed with Dr. Cohen, arguing that vaccination strategy should be considered part of the multifaceted program of controlling COVID-19 and noting that for a disease that is highly transmissible between people it is important to optimize population protection. This approach must consider how to best use scarce monoclonals, vaccines, and (soon) antiviral drugs, and how to deploy these tools to maximize population benefit.

Developing Vaccines Against New Variants vs Boosting with Existing Vaccines

Dr. Corey asked for perspectives on the question of whether the criteria for boosting vaccination should be based on severe disease outcomes or mild-to-moderate disease prevalence, noting the costs associated with revaccinating the entire US population. Dr. Glenn agreed with the importance of efficacy against severe disease, and observed that there are still relatively few severe cases (b) (4)) and conclusions on protection against severe disease will be difficult to draw without many more cases. He noted that the prevalence of moderate disease in (b) (4) that additional severe cases will be observed over time.

Dr. Corey raised the issue of optimizing in the short-term vs. the long-term. He noted that SARS-CoV-2 has already demonstrated (in 501Y.V2 variant) the ability to almost completely escape neutralization. This ability suggests that a serial focus on individual variants could continue repeatedly, and if vaccines were modified to follow this evolution the result could be an original antigenic sin effect analogous to what is observed with influenza, which in the long-run may not be the best approach. This suggests it is important to develop a deeper scientific understanding, particularly of protection against severe disease, that may determine that always chasing viral evolution with new vaccines is not necessary or optimal.

Dr. (b) (6) also (b) (5) Dr. (b) (5) agreed with Dr. (b) (6) that (b) (5)

Dr. (b) (6) observed that (b) (4) trial (b) (5)

(b) (5) Dr. (b) (6) suggested (b) (5) Dr. (b) (6) (b) (5) Dr. (b) (6) noted (b) (5)

Dr. Glenn described results from (b) (4) Phase influenza trials that reinforce the potential of eliciting sufficiently broad immune responses to provide protection against different variants, particularly when the vaccine exposes conserved epitopes. However, despite these observations, Dr. Glenn reiterated that (b) (4) has seen a decline in efficacy against the 501Y.V2 variant and believes that this will continue to be an issue because of waning immunity, motivating development of vaccines matched against variants.

Dr. Lowy suggested that boosting with existing vaccines may be a viable strategy to protect against new variants. However, if a change in composition generated an even higher level of efficacy against all known variants, that would be an even better outcome. [Note that at the last meeting Drs. Moore and Sigal showed that Ab responses raised by 501Y.V2 infection neutralized ancestral viral strains better than the opposite comparison, which may suggest that vaccines against 501Y.V2 would provide better protection against ancestral strains than current vaccines do against 501Y.V2.] The FDA's effort to make compositional changes as easy as possible may facilitate development of such vaccines.

In response to these observations, Dr. (b) (6) (b) (5) Dr. (b) (6) noted that (b) (5) various companies (b) (4)) (b) (5) Dr. (b) (6) (b) (5) (b) (4) , (b) (5) Dr. (b) (6) (b) (5) Dr. (b) (6) noted that in (b) (4) (b) (5)

Dr. Corey suggested that a catalog of immunogenicity studies would be valuable to understanding the data that will be available to inform these decisions. Dr. Mascola shared that such a catalog will be developed by the USG in collaboration with companies and with the UK and CEPI. Dr. Emily Erbelding noted that studies with variant-matched boosts are still in the planning phases, and results are likely months away.

Next Steps

Dr. Corey challenged the group the think more about what the go/no-go criteria should be for introducing new vaccines in response to variants. Will a correlate of protection from the mRNA vaccines (which would be an Ab correlate) be the key to developing criteria, e.g., neutralization of variants at the level that corresponds to protection against the ancestral strain? Dr. Corey suggested continuing the discussion with greater granularity.

Given the WG conversations on this topic, some questions for the group to consider further:

- When will data inform whether immunity to ancestral strains protects against serious outcomes (hospitalization, death) from known variants?
  - Natural immunity?
  - Vaccine-derived immunity?
- Generally speaking, a lack of cross-protection against serious outcomes may be the most compelling rationale for updating vaccines in response to new variants. How, and how quickly, can this be assessed for new variants?
  - During the follow-up phase of existing large efficacy trials?
  - Through observational cohorts of vaccine recipients?
  - Through routine surveillance?
- If there is good cross-protection against serious outcomes, how valuable is it to vaccinate to protect against mild disease with variants, particularly if that comes at the expense of expanding vaccination?
  - What are the potential immunological risks of serial vaccination targeting variants (as seen with flu)? How can those risks be assessed (e.g., in the NIAID/Moderna and UK boost studies)?
- What are the costs in time and complexity of introducing wide-scale naïve vaccination and/or boosting with new vaccines?
  - What, if any, are the implications for vaccine confidence?

WG members are encouraged to reach out any time with comments and suggestions. Scheduling is in progress for a WG on the epidemiological impact of new variants, with a presentation from Chris Murray of the Institute for Health Metrics and Evaluation.

Appendix A: Participants List

WORKING GROUP MEMBERS

Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI), National Institutes of Health (NIH)*

Paula Annunziato, MD, *Vice President, Vaccine Clinical Development, Merck*

Ann Arvin, MD, *Professor of Pediatrics and Microbiology & Immunology, Stanford University*

Susan Buchbinder, MD, *Director of Bridge HIV, San Francisco Department of Public Health, and Professor, UCSF*

Larry Corey, MD, *Professor and Principal Investigator, University of Washington and HIV Vaccine Trials Network, and Past President and Director, Fred Hutchinson Cancer Research Center*

Greg Glenn, MD, *President, Research & Development, Novavax*

Barton Haynes, MD, *Professor of Medicine and Director of the Human Vaccine Institute, Duke University*

Peter Hotez, MD, PhD, *Dean for the National School of Tropical Medicine, Baylor College of Medicine, and Director, Texas Children's Center for Vaccine Development*

Antonio Lanzavecchia, MD, *Director, Immune Regulation, Institute for Research in Biomedicine*

Peter Marks, MD, PhD, *Director, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA)*

John Mascola, *MD*, *Director, Vaccine Research Center, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Paul Offit, MD, *Professor, University of Pennsylvania, and Director, Vaccine Education Center, Children's Hospital of Philadelphia*

Michael Santos, PhD, *Associate Vice President, Science, Foundation for the NIH (FNIH)*

Hanneke Schuitemaker, PhD, *Global Health, Viral Vaccine Discovery and Translational Medicine, Johnson & Johnson's Janssen Vaccines*

Brett Tolman, MA, *Strategy Manager, Deloitte*

INVITED PARTICIPANTS

Myron Cohen, MD, *Director for Global Health & Infectious Diseases, University of North Carolina (UNC) School of Medicine*

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH*

Alan Embry, PhD, *Chief, Respiratory Diseases Branch, NIAID*

Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, NIAID, NIH*

Clint Florence, PhD, *Program Officer, Research Resource Section, OBRR, DMID, NIAID, NIH*

Ellen Gadbois, PhD, *Program Lead, Biosafety, Biosecurity, and Emerging Biotechnology Policy Division, Office of Science Policy, NIH*

Paul Gillard, MD, *Senior Director, Clinical R&D, GSK*

Antonio Gonzalez-Lopez, MD, *Global Clinical Head, COVID-19 Vaccine US Program, AstraZeneca*

Holli Hamilton, MD, MPH, *Senior Medical Officer, BARDA*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis*

Randall Hyer, MD, PhD, *Senior Vice President, Global Medical Affairs, Moderna, Inc.*

Nicole Kallewaard, *Microbial Sciences, BioPharmaceuticals R&D, AstraZeneca*

Joanne Lumsden, PhD, *Senior Scientific Program Manager, Drug Development Partnership Programs, NCATS, NIH*

Mary Marovich, MD, *Director, Vaccine Research Program, NIAID, NIH*

Kathy Neuzil, MD, MPH, *Professor, University of Maryland School of Medicine*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Vivek Shinde, MD, MPH, *Vice President, Vaccine Clinical Development, Novavax*
Gale Smith, PhD, *Vice President of Vaccine Development, Novavax*
Mark Sotir, PhD, *Epidemiologist, CDC*
Jenny Svarovskaia, PhD, *Senior Director, Clinical Virology, Gilead Sciences*
Natalie Thornburg, PhD, *Lead Microbiologist, Respiratory Viruses Branch, CDC*
Kanny Wan, PhD, *Research Scientist, NCATS*
Roland Zahn, PhD, *Senior Scientific Director, Preclinical Immunology, Viral Vaccines, Janssen*

FNIH STAFF
Stacey Adam, PhD, *Director, Cancer, FNIH*
Stephanie James, PhD, *Senior VP of Science, FNIH*
Joseph Menetski, PhD, *Associate VP of Research Partnerships, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Dana Carluccio, PhD*, Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From 566300 to Everyone: 12:14 PM

Correction to consider...JNJ reported 57% efficacy on mod-severe...did not report the n for mod-severe, or severe alone...NVAX was 49% with HIV+ and HIV-, 60% without HIV positive...1 severe case in placebo...more to come, with a second analysis with larger numbers

NVAX primary endpoint was all, ie mild/mod/severe

Another point to consider

NVAX efficacy, 96% against matched strain, 85% against UK variant, 60% agains SA variant in same populations

From Peter Hotez to Everyone: 12:14 PM

I have a comment

From Larry Corey to Everyone: 12:16 PM

i have a discussion question to raise

From Paul Gillard (GSK) to Everyone: 12:19 PM

The epidemiological data seems to indicate that variants dominate eventually (UK B117.V1, SA B117.V2); could we for once be one step ahead of this virus and switch before variants become a real inevitable problem? or have dose 1 and dose 2 with different composition (complex logistics).

From 566300 to Everyone: 12:20 PM

I have a comment on MN

From mscohen to Everyone: 12:29 PM

Of course, if mabs work for variants it will support vaccines that generate a variety of variants. Mabs give quik and immediate answers

From annarvin to Everyone: 12:32 PM

On the flu model, what is the time line to prepare for boosting with a variant-based vaccine? how to we anticipate yet another variant?

From mary marovich to Everyone: 12:33 PM

suggestion discussion re: one threshold for action with a VoC -could be the trajectory/pace of new CoV rapid dominance in a county or population? suggesting fitness advantage

From Antonio Gonzalez-Lopez to Everyone: 12:36 PM

What will the pathway for the development of new variants vaccines?. Immuno studies, only pre-clinical or efficacy studies?

From mary marovich to Everyone: 12:44 PM

https://www.fda.gov/media/142749/download

From Paula Annunziato to Everyone: 12:45 PM

Thank you for sharing the link to the guidance!

From Antonio Gonzalez-Lopez to Everyone: 12:53 PM

Thank you for sharing

From Paul Gillard (GSK) to Everyone: 01:00 PM

Thank You to all.

CONFIDENTIAL INFORMATION

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard a presentation on ACTT-3 preliminary results and received status updates from the Master Protocol Subgroup (MPSG), including updates to ACTIV-6, and on the TX-Clinical WG manuscripts.

ACTT-3 Preliminary Results

Dr. John Beigel, NIAID

Overview

ACTT-3 studied the impact of interferon therapy in combination with (b) (4) to address a growing volume of research suggesting that IFN-beta 1 alpha is a promising therapeutic against COVID-19. ACTT-3 is designed similarly to ACTT-1 and focuses on a hospitalized population of 969 adult patients with a recent positive COVID-19 test and evidence of lower respiratory tract disease. Patients were enrolled in five countries, with the majority of sites within the U.S. Patients were randomized to either the IFN-beta 1 alpha plus remdesivir or placebo plus (b) (4) arms and received IFN-beta 1 alpha or placebo subcutaneously and an infusion of (b) (4) on Days 1, 3, 5, and 7.

ACTT-3 used the 8-point ordinal scale to define its clinical endpoints and only enrolled patients within Ordinals 4, 5, and 6. On September 4, (b) (5)

Primary Endpoint

ACTT-3's primary endpoint is time to recovery (i.e., how quickly patients in Ordinals 4, 5, and 6, can enter Ordinals 1, 2, or 3). The median time to recovery for patients in both the intervention and placebo arms was 4 days in Ordinal 4 and 5 days in Ordinal 5. Kaplan-Meier curves for the intervention and placebo arms of both ordinals directly overlay each other. The median time to recovery within the Ordinal 6 IFN-beta 1 alpha study arm was not estimable, compared to 6 days in the placebo arm. However, the Ordinal 6 intervention curve was significantly lower than the placebo curve and forest plot analyses showed a lack of signal related to duration of symptoms within the intervention arm, suggesting that the intervention is not providing any symptom benefit. The numbers of patients in each Ordinal study arm are small, but the current effect trend is concerning.

Secondary Endpoints and Outcomes

The key secondary endpoint is ordinal score at Day 15. Comparing study arms using ordinal scale data resulted in an odds ratio estimate of 1.10 and a p-value of 0.467, which suggests a lack of benefit on this endpoint. Another secondary outcome assessed oxygen need (i.e., comparing baseline oxygen to current need and whether patients had to receive supplemental oxygen). Patients receiving IFN-beta 1 alpha were administered supplemental oxygen for on average 6 days, whereas patients receiving placebo were on oxygen for 7.5 days. Approximately 51 percent of the intervention arm population exhibited new oxygen use, compared to 57 percent of the placebo arm population.

ACTT-3 also assessed mortality at Day 29 and found that 2 patients died in the Ordinal 4 intervention group compared to none in the placebo group. For Ordinal 5, the mortality rates of intervention and placebo groups were both 3% and for Ordinal 6 were 21 percent (intervention) compared to 12 percent (placebo); Ordinal 6 patients in the intervention arm were also more likely to experience adverse events, including serious AEs, with a rate of 60 percent (intervention) compared to 26 (placebo), and the primary SAE of respiratory distress (29 percent intervention and 9 percent placebo).

At baseline, no patients required mechanical ventilation. During the study, approximately 54 percent of the Ordinal 6 intervention group were placed on mechanical ventilation, compared to 15 percent of the placebo group. Ordinal 6 patients were more likely to progress to worse ordinal scores by Day 28 in the intervention versus placebo groups (60 vs. 18 percent). Using shift plots, ACTT-3 researchers visualized the reduction or worsening in symptoms over time and found that Ordinal 6 patients receiving IFN-beta 1 alpha worsened, whereas placebo patients recovered. Interestingly, the Ordinal 6 placebo arm exhibited a median duration of symptoms of 9 days, compared to 8 days in the intervention group. The ACTT-3 team considered the possibility that patients within the intervention and placebo arms may differ significantly but overall numbers are too small to draw major conclusions without further analyses.

The ACTT-3 team assessed CRP protein as another secondary outcome and found that patients that worsened during the study exhibited consistently higher CRP levels than patients that recovered, suggesting that worsening patients may have entered the study in a more inflamed state. They also found that d-dimer levels were consistently higher in the worsening patient group receiving IFN-beta 1 alpha, compared to the placebo group which showed similar d-dimer levels for both patients that worsened or recovered.

Conclusions

IFN-beta 1 alpha, in combination with (b)(4), does not improve outcomes within the hospitalized population. ACTT-3 results suggest that some patients may worsen with IFN-based treatments, despite many studies suggesting that IFN treatments help COVID-19 patients. ACTT-3 results should not be used to inform IFN treatment strategies for outpatients or to assess how COVID-19 will impact patients receiving IFN treatments for chronic conditions. The ACTT-3 team will soon publish a manuscript detailing the final analyses and results of the study.

Discussion

Implications of Results

Dr. (b)(6) noted that (b)(5). Dr. (b)(6) noted

(b) (5) with Drs. (b) (6) and (b) (6).

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Dr. (b) (6) (b) (5). Dr. (b) (6) noted (b) (5)

Definitions and Procedures

Dr. (b) (6) (b) (5). Dr. (b) (6) noted (b) (5)

Dr. (b) (6) (b) (5). Dr. (b) (6) (b) (5)

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5/-6):

ACTIV-1: Immunomodulators (Inpatient Phase III)

ACTIV-1 has activated 41 sites (with five satellite sites) and (b) (4); three sites are now activated in Peru. The ACTIV-1 team has selected an additional 86 sites and aims to activate 20 new sites in the next 4 weeks (including in Argentina and Brazil).

The team is currently finalizing responses to FDA comments regarding the statistical analysis plan and aims to submit tomorrow. The team continues to address complications with the (b) (4) sub-study, particularly related to how sites will assess disease progression.

The team is also discussing how to approach the possibility of (b) (4) being incorporated into COVID-19 standard of care. The team has proposed that patients can receive (b) (4) after randomization, but not before. If (b) (4) becomes standard of care, the team may need to incorporate an active control arm into the study.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has completed enrolling patients into the Brii Bio arm and has enrolled the first patients for each Version 3.0 agent (AZ IM and IV, inhaled Synairgen, and oral camostat). Dr. Currier confirmed that ACTIV-2 allows only high-risk patients to receive IV drugs, whereas all patients who are ineligible for current EUA agents will be randomized to the non-infused arms.

The ACTIV-2 team submitted Version 4.0 of the protocol yesterday, which will include agents from RU-BMS and BI. Guidelines committees have endorsed the use of the (b) (4) antibody combination as standard of care for high-risk populations. The team is currently discussing how to incorporate standard of care antibodies into future study arms. The team also aims to assess agents against emerging variants to ensure the agents can maintain activity.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

ACTIV-3 has activated 62 sites and (b) (4). Sites are now open in Poland, Singapore, Switzerland, and Denmark; additional sites are registered in India and the UK.

The ACTIV-3 team is now preparing for DMSB review for Version 2.0 agents (Brii Bio and GSK Vir) on March 1. (b) (4) The team is in discussions with (b) (4) to incorporate their agents in future versions of ACTIV-3, although MP's product availability will likely delay incorporation of its agent by 1 month. Before taking on these agents, the team aims to review the implications of the (b) (4) Vir results for the approach to treating inpatients with mAbs. The team continues to work with (b) (4) to incorporate aviptadil into the ACTIV-3b study; the protocol was submitted on February 22 and the team aims to launch this study during the first week of March.

The Agent Prioritization Committee approved the advancement of Pfizer's protease inhibitor into ACTIV-3; Pfizer's Phase I study will provide a final readout during April and this agent will likely be incorporated into ACTIV-3 at that time.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4A (hospitalized) will soon begin enrollment into its therapeutic heparin plus P2Y12 arm (therapeutic high dose of heparin +/- P2Y12 inhibitors for moderate COVID-19 patients and low prophylactic doses of heparin +/- P2Y12 inhibitors for severe COVID-19 patients). The team has submitted its publication to the New England Journal of Medicine.

ACTIV-4B (pre-hospitalized) has activated 27 sites and (b) (4). The team has initiated a pilot study of low-touch enrollment in Illinois and Massachusetts in parallel with enrollment at conventional sites.

ACTIV-4C (post-hospitalization) has (b) (4) and is working to activate more sites.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

ACTIV-5 has activated 17 sites and (b) (4). The ACTIV-5 team is in discussions with an additional 33 sites. BET-B is currently on hold because of a manufacturing qualification failure; however, the manufacturer recently shared that this failure did not impact the product, which is ready for use. The team will ask for IRB approval to proceed with the BET-B trial.

Discussion

Dr. Adam asked about the timeline to select agents for BET-C and BET-D. Dr. Beigel noted that ACTIV-5 is taking a systems biology approach to identify new agents, particularly agents that address a current unmet need. The team is currently discussing evaluating danicopan in BET-C; danicopan is a complement pathway inhibitor. For BET-D, the team is in discussions with (b) (4) agent, which has been studied in relation to acute respiratory distress syndrome with promising results in severe populations.

ACTIV-6: Pragmatic Platform Trial (Outpatient)

ACTIV-6 is an outpatient, pragmatic platform trial to evaluate generic and widely available drugs for COVID-19 treatment. The first drug tested in ACTIV-6 will be ivermectin, which will be supplied by Ingenus along with corresponding placebo. ACTIV-6 has not yet received funding but is proceeding as if it will be funded as intended. The ACTIV-6 team is currently selecting endpoints that will provide the best benefit to patients (i.e., how can patients feel better faster), while also assessing regulatory needs. The team has included a primary symptomatic endpoint and a secondary hard clinical outcomes endpoint; these endpoints may not suffice for EUA approach, but the team has decided that EUA is not the study's main goal. The team aims to finalize a protocol draft this week and begin pre-IND meetings next week.

PCORnet will be the lead network with other networks (e.g., NHLBI/SIREN) expected to collaborate. The team has identified 80 domestic sites to start the trial. The team has also developed a draft trial synopsis and aligned on a governance structure that includes the ACTIV-2/3 Trial Oversight Committee and the PCORnet HERO-HCQ DSMB. The ACTIV-6 Prioritization Committee has been launched to discuss agents for future ACTIV-6 study arms.

Discussion

Dr. Buchman asked how ACTIV-6 will manage and validate data, noting that this is the only USG platform tasked with assessing approved agents and thus may become the prototype for others to come. Dr. Adam noted that Dr. Christopher Lindsell is modeling the ACTIV-6 trial design after other ongoing trials, such as TREAT NOW and influenza trials, and that he is also developing a database to enable sharing of ACTIV-6 data with DSMBs and other trial teams. Dr. Adam added that she can invite the ACTIV-6 team to present during a future TX-Clinical WG meeting.

TX-Clinical WG Manuscript Updates

Both TX-Clinical WG manuscripts are finalized and the Manuscript Subteams are currently discussing which journal to target for the paired submission.

Appendix A: Participants List

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Alex Sorosa, *Business Analyst, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Neil Aggarwal to Everyone: 01:23 PM

John - thank you. Very interesting data, Can you comment on con meds (specifically steroid use) among ord 6?

From Eric Hughes to Everyone: 01:32 PM

Thank you John! Greatly appreciated.

From Timothy Buchman to Everyone: 01:33 PM

Terrific presentation. There may be great insight into the pathobiology of the illness from this and the other studies you have shepherded.

From Eric Hughes to Everyone: 01:38 PM

Good work Sam!

From Sam Bozzette to Everyone: 01:46 PM

thanks Eric. Team has been swimming upstream the whole way

From Timothy Buchman to Everyone: 01:47 PM

Congratulations on the progress towards publication, Andrei!

From Timothy Buchman to Everyone: 01:53 PM

A remark from the front lines. Those in ordinal 7 are doing worse than 4 months ago.

From Neil Aggarwal to Everyone: 01:54 PM

Tim - any speculation on why - longer before intubation/MV is utilized?

From Timothy Buchman to Everyone: 01:54 PM

While numbers are lower, the general condition of the patients is worse, their trajectories are longer, the outcomes less happy.

We are unsure. All we know is that in informal discussions on listservs, this is now the common experience.

It may be that the "readily supportable" are not missing the ICU entirely.

In any event, these patients are now having stays measured in weeks->months.

are *now* missing the ICU, sorry for typo above.

From Eric Hughes to Everyone: 01:57 PM

Is there any variant correlation?

From Timothy Buchman to Everyone: 01:59 PM

Too soon to tell.

For ACTIV-6, is there a well-developed strategy around the data enclave?

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard status updates from its Master Protocol Subgroup (MPSG), Agent Prioritization Subgroup (APSG), and TX-Clinical Manuscript Subteams and discussed a new ACTIV initiative regarding biospecimen prioritization.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5).

ACTIV-1: Immunomodulators (Inpatient Phase III)

ACTIV-1 has activated 24 sites and (b) (4) The ACTIV-1 team has selected an additional 81 sites (59 U.S. and 33 ex-U.S.). The team has received regulatory approval in Argentina and Peru and anticipates to soon receive approval in Brazil and Mexico; the goal is to begin activating Latin American sites during mid-January.

The ACTIV-1 team received IRB approval for its master protocol amendment and is awaiting final comments from FDA. The amendment streamlines the patient enrollment process and enables co-enrollment with ACTIV-4 (which is currently on hold, pending ACTIV-4A DSMB review).

The team will meet with the ACTIV-1 DSMB today to perform a futility review of data collected from the first (b) (4).

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has activated 90 sites and (b) (4). ACTIV-2 continues to engage in activities to improve the diversity of the enrolled patient population.

The ACTIV-2 team has begun enrolling patients into Version 2.0 of the protocol, which includes the Brii Bio combination mAbs. The team is developing Version 3.0 of the protocol, which will include the IM- and IV-administered agents from AZ, oral camostat from Sagent, and the inhaled IFN-beta agent from Synairgen. Once Version 3.0 is complete, the team will develop Version 4.0, which will include the SAB agent (currently under review by FDA).

In collaboration with NIAID, the team has developed a sub-study to investigate the effects of vaccination in the context of mAb treatment. Patients who elect to participate in the sub-study will be administered open-label Moderna vaccine (90 days after receiving mAb treatment, per CDC guidelines) and the team will compare immune response data between mAb-treated and control groups.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

ACTIV-3 has activated 29 sites and (b) (4). The ACTIV-3 team has begun enrolling patients into Version 2.0 of the protocol, which includes agents from (b) (4). During January, the ACTIV-3 DSMB performed an early safety review for data collected on the first 20 patients administered either the (b) (4) agent. In addition, the team expects to soon begin activating sites in other countries, which has been waiting to review the DSMB safety review data before agreeing to participate.

(b) (5) (b) (4), and is in (b) (5) . In addition, a (b) (4) (b) (5) (b) (4)

In collaboration with the PETAL network, the team has developed an ACTIV-3 sub-study (i.e., ACTIV-3B) to investigate the treatment of (b) (4) and (b) (4) for COVID-19-mediated acute respiratory distress syndrome (ARDS) in patients requiring high-flow oxygen or mechanical ventilation. This study includes a new primary endpoint that is a composite of survival and recovery time to be analyzed at 90 days post-administration.

Discussion

Dr. Jacqueline Kirchner inquired whether (1) ACTIV-3 will sequence COVID-19 samples in order to determine the specific strain found in each patient and (2) whether it will also investigate vaccination-related effects (similarly to the ACTIV-2 sub-study). Both ACTIV-2 and -3 are sequencing upper respiratory compartment samples; ACTIV-3 is now updating its CTAs in order to share any variant-related findings with sponsor companies. ACTIV-3 will also evaluate possible effects of vaccination in its study arms. OWS has initiated a project to test agent potency against multiple variant strains in order to identify resistance-causing variants; it has also initiated a project to interrogate the impact of mAbs on vaccines as well as vaccines on mAb treatment.

Dr. Stacey Adam will invite the Preclinical Therapeutics WG to present during a future TX-Clinical WG meeting on collaborations with NIAID related to both variant resistance and vaccination effects.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4's in-hospital protocol (4A) has activated 45 sites and (b) (4). ACTIV-4A is also collaborating with partner trials, which brings the total number of activated sites to 100 and (b) (4)). The ACTIV-4A DSMB performed a futility assessment on the first round of data generated and found that the cohort with highest disease severity did not have adequate results to proceed and thus was discontinued in the study. The ACTIV-4A team is now preparing a publication detailing the results of this initial DSMB review. The team is also finalizing the updated ACTIV-4A protocol, which now includes a P2Y12 arm in the heparin study; a specific P2Y12 agent will be selected by each site depending on availability.

The ACTIV-4 pre-hospitalized protocol (4B) has activated 10 sites and (b) (4) . The ACTIV-4B team aims to soon begin leveraging CVS MinuteClinic sites for the trial.

The post-hospitalized protocol (4C) is expected to launch soon. The ACTIV-4C team received safe-to-proceed notification from the FDA and also received its first shipment of drug supply this week.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

ACTIV-5 has activated nine sites and (b) (4) . The ACTIV-5 team aims to enroll 100 patients per study arm in both the BET-A (risankizumab) and BET-B (lenzilumab) trials; however, enrollment has been very slow. The team recently received funding from OWS, which may be used to engage in activities to bolster enrollment. The team is also continuously reviewing new agents for future BET trials.

Agent Prioritization Subgroup Updates

During Waves 2 and 3, the APSG has advanced 16 agents (3 antivirals, 4 immune modulators, and nine nAbs) into ACTIV master protocols, designated 25 agents as promising but requiring follow-up, deferred 44 agents, and dropped 80 agents. The APSG continues to review 10 to 12 new agents each week.

Cross ACTIV Biospecimen Prioritization

Many ACTIV trial teams have received requests regarding the usage of residual samples for other projects. Thus, ACTIV leadership initiated discussions on this topic and identified the need for a policy governing the long-term use of biospecimens collected during ACTIV trials and for a unified governing body (either cross-ACTIV or trial-specific) to handle these requests. ACTIV-1, -2, -3, and -4 trial teams have recommended developing a cross-ACTIV governance structure—with representation from all trial teams and various ACTIV WGs (including TX-Clinical WG)—to best support biospecimen prioritization for key scientific objectives. Next steps for this effort include ACTIV facilitators creating an inventory of residual samples that could be prioritized for future studies and developing a proposal for the cross-ACTIV governance committee structure.

Discussion

The biospecimen prioritization effort may have additional benefit both within and outside ACTIV. Dr. Timothy Buchman emphasized that this effort could provide invaluable long-term infrastructure that enables the study of many different infectious diseases and serves as a template for other projects. Dr. Neil Aggarwal added that this resource could help dissect the immense heterogeneity observed in COVID-19 in order to better match patient subtypes to the most appropriate treatment.

Dr. Walter Koroshetz noted that he is involved in a similar repository-developing project focused on COVID-19 recovery and recommended regular interfaces between this effort and that of ACTIV to align strategies and best practices.

TX-Clinical WG Manuscript Updates

The Agent Prioritization Manuscript and Master Protocol Manuscript Subteams have both developed complete working drafts and are now performing a final review of those drafts before sharing them with the TX-Clinical WG for review (likely to occur next week). Both Subteams aim to submit these manuscripts during January.

Appendix A: Participants List

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Helen Chen, PhD, *Consultant, Deloitte*

Evan Appell, *Consultant, Deloitte*

Alex Sorosa, *Business Analyst, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Neil Aggarwal, NHLBI to Everyone: 01:40 PM

This is a great development.

Willing to help on this effort as needed.

High-Level Meeting Summary

The Vaccines Working Group (WG) convened to discuss a proposed clinical trial to assess the impact of vaccines on infection, viral load, and transmission.

Impact of Vaccines on Transmission

During the last meeting, Vaccines WG members identified future priorities for the Vaccines WG, one of which was to consider the impact of vaccines on transmission. The Clinical Trials Subgroup discussed this topic during the 18 November meeting and Drs. (b) (4), (b) (6) and (b) (4), (b) (6) were invited to present the proposed (b) (4) the (b) (4)) to the WG for discussion. In addition, Dr. Stephanie Schrag offered to share some of the CDC's planned and proposed studies to assess the impact of vaccines on transmission. Dr. Doug Lowy explained that input from this meeting will inform his presentation to the ACTIV Leadership Team the WG's views.

(b) (4)

2020_12_(b) (4)
[redacted] Summary_1030

Uncertainty of (b) *for Current Vaccines*

To date, Moderna and Pfizer have each produced mRNA-based vaccines that are effective in preventing COVID-19; Pfizer's BNT162b2 has received Emergency Use Authorization (EUA) and Moderna's mRNA-1273 will likely receive EUA soon. Both Moderna and Pfizer designed their phase 3 trials primarily to study vaccine efficacy against COVID-19 disease (b) (4)); however, vaccine efficacy can also be characterized against susceptibility (b)) (i.e., infection of an exposed person even without disease) and against infectiousness (b)) (i.e., onward transmission from an exposed person to another person). Both Moderna and Pfizer assessed (b) as a secondary objective using serology; however, seroconversion is a low sensitivity biomarker that can miss a large fraction of asymptomatic infections and insights will be limited by infrequent sampling. Further, neither Moderna nor Pfizer collected (b) information, which requires robust contact tracing methods for direct assessment or unbiased virological sampling. Thus, phase 3 vaccine trials will not answer the question of whether vaccines prevent secondary infections.

Preclinical studies indicated some possibility for transmission from NHPs that were protected from disease by vaccination: sub-genomic RNA (a putative measure of infectious virus) in nasal and bronchial samples from macaques showed some animals shed high virus titers in nasal samples shortly after challenge; nasal titers were vaccine dose dependent.

Additionally, the availability of two EUA-issued vaccines will decrease the ability to initiate new placebo-controlled trials and thus the window to complete a placebo-controlled transmission-focused vaccine study is rapidly closing.

(b) (4) *Clinical Trial Overview*

(b) (4) clinical trial, a Phase IIB randomized-controlled trial in US college students to assess (b) (4) vaccine and determine whether this vaccine can prevent onward transmission of COVID-19.

The two specific aims of the (b) (4) clinical trial are to (1) determine vaccine efficacy against transmission of SARS-CoV-2 infection and (2) to evaluate a dose-sparing regimen of the vaccine. The rationale to enroll college students is that they have high asymptomatic infection rates, increased secondary infections per primary infection (due to high-density living situations and behavioral factors), and will generally not be prioritized for vaccination during the spring 2021 semester.

Further, the (b) (4) clinical trial will help provide answers to the public, policymakers, and schools for the following questions:

- If I get the vaccine, do I need to continue wearing a mask and social distancing? Should I quarantine if exposed to COVID-19? Will my family be better protected as a whole?
- How should people at low risk for severe disease but high transmission risk (e.g., young individuals) be prioritized for vaccination?
- When making school policy for Fall 2021, should vaccination be required for attendance?

Statistical models of vaccine efficacy suggest that vaccines with higher (b) will markedly reduce the incidence of COVID-19 infections and deaths (49.3% reduction in infections for 50% vs. 0% (b) vaccine and 50.9% reduction in deaths for 50% vs. 0% (b) vaccine). Clear evidence of (b) may play a key role in promoting vaccine uptake in groups with low risk perception.

Necessity for the (b) (4) *Clinical Trial Design*

Seroconversion assays in existing phase 3 trials are inadequate for assessing prevention of infection and do not directly assess transmission. In addition to the 20-40% of asymptomatic infections that do not result in acute seroconversion, two studies found seroreversion after 8 weeks among a significant fraction of acute seroconversions; blood draws for serologies in phase 3 trials are several months apart. One of those studies also showed no significant difference in viral shedding between seropositive and seronegative patients.

A randomized clinical trial is the best method to assess vaccine effects on transmission. Observational studies require significantly longer timelines to gather and analyze collected data and provide lower quality evidence.

(b) (4) included the second aim to evaluate a dose-sparing regimen (b) (4) in order to address the potential challenge of vaccine scarcity.

Data shared by Dr. (b) (4), (b) [redacted] shows that the (b) (4) [redacted] vaccine appear to achieve equivalent levels of binding antibodies in young adults.

Trial Objectives

The primary objectives of the (b) (4) [redacted] clinical trial are to (1) (b) (4) [redacted] (b) (4) [redacted]), (2) (b) (4) [redacted] and (3) (b) (4) [redacted] (3) (b) (4) [redacted] and (4) (b) (4) [redacted]

Study Population

The (b) (4) [redacted] clinical trial (b) (4) [redacted]

Study Design

The (b) (4) [redacted] clinical trial study design (shown below) involves (b) (4) [redacted]

(b) (5) [redacted]

Contact Tracing

(b) (4) [redacted]

(b) (4)

Sample Size Rationale
(b) (4) estimates that (b) (4)

Site Selection
(b) (4) has performed informational interviews (b) (4)

Timeline
The proposed timeline is shown below.

(b) (4)

CDC's Upcoming Transmission-Focused Studies
Dr. Stephanie Schrag

CDC is planning an observational study to evaluate post-vaccine COVID-19 transmission in an existing cohort of 5,000 healthcare workers and first responders at seven sites across the U.S. This study will involve collecting respiratory specimens weekly (for PCR) and blood periodically. CDC will primarily obtain samples from the study participant, but will also collect samples from all members of the participant's household if the study participant tests positive for COVID-19.

This study will run for 1 year, with the potential to preliminarily estimate VE_S at 6 months, depending on vaccine coverage and efficacy against infection; the study will likely not be powered to directly evaluate prevention of secondary transmission, but will be able to evaluate the combination of VE_S and VE_I. This study is structured similarly to an ongoing study in the UK, which has (b) (4) healthcare worker participants, but the UK study will collect specimens less frequently.

CDC also has studies planned to start in spring that will specifically evaluate the potential for transmission given infection, which will be investigated using the case ascertain method to evaluate index infection cases who are or are not vaccinated and are likely the first infected member of their households. The subsequent process is to enroll the household to track secondary infections for a time-limited period. Finding index cases and reaching households quickly enough to initiate molecular testing will be the challenge in this model; CDC is now partnering with institutions in the respective study jurisdictions to develop early detection systems in order to quickly identify breakthrough cases, which may be rare given the demonstrated efficacy of vaccines so far.

Dr. (b) (6) noted that these studies (b) (4), (b) (5)

Knowing that observation studies (b) (4), (b) (5) CDC is proposing (b) (4), (b) (5) (b) (4), (b) (5) Dr. (b) (6), who will disseminate the information to the Vaccines WG [embedded below]. She noted that (b) (4), (b) (5)

Phase III add-on
concept note_v4_14

Discussion

(b) (4) *Clinical Trial's Study Design Considerations*

Dr. (b) (6) noted that (b) (4) s proposed study appears (b) (4), (b) (5) Dr. (b) (6) noted that (b) (4), (b) (5) In addition, (b) (4), (b) (5)

(b) (4), (b) (5) Dr. (b) (6) noted that the (b) (4) clinical trial's study design (b) (4), (b) (5) Dr. (b) (6) added that the (b) (4) study (b) (4), (b) (5)

Dr. (b) (6) inquired whether the (b) (4) team (b) (4), (b) (5) Dr. (b) (6) responded that (b) (4) (b) (4), (b) (5)

Dr. (b) (6) noted that (b) (4), (b) (5) . (b) (4), (b) (5) He added that the (b) (4) study (b) (4), (b) (5) Dr. (b) (6) (b) (4), (b) (5)

Generalizability of the (b) (4) Clinical Trial

Dr. (b) (6) inquired about the generalizability of the (b) (4) clinical trial (b) (4), (b) (5) . Dr. (b) (6) noted that there are (b) (4), (b) (5) Dr. (b) (6) noted that (b) (4), (b) (5) Dr. (b) (6) (b) (4), (b) (5)

Evaluating Vaccines (b) (4), (b) (5)

Dr. (b) (6) (b) (4), (b) (5) n

(b) (4), (b) (5) Dr. (b) (6) noted that the (b) (4) T clinical trial (b) (4), (b) (5) Dr. (b) (6) suggested that opening enrollment (b) (4), (b) (5) Dr. (b) (6) noted that (b) (4) is collecting data on (b) (4), (b) (5) and will be setting up a (b) (4), (b) (5) of clinical trials. Dr. (b) (6) emphasized the importance of completing a clinical trial (b) (4), (b) (5) and noted that the (b) (4) trial (b) (4), (b) (5)

Additional Comments

Dr. Myron Cohen noted that (b) (4) ran a large household-based study that aimed to determine whether treated index cases were infecting others in their households; thus the therapeutics and vaccine research communities are in alignment that understanding transmission is critical.

Dr. Cohen noted that public health policy depends on all types of data, including observational, ecological, and clinical trial data, in order to make informed decisions. Often a large weight of evidence from multiple sources are required to change guidance, as exemplified by the HIV research community's experience, and the data sources should not be viewed as exclusive of one another.

Next Steps

Dr. Santos noted that Dr. Lowy will be presenting to ACTIV Leadership on December 16 and invited participant to share any remaining thoughts on the impact of vaccines on COVID-19 transmission via email.

Appendix A: Participants List

WORKING GROUP MEMBERS

Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI), National Institutes of Health (NIH)*

Paula Annunziato, MD, *Vice President, Vaccine Clinical Development, Merck*

Ann Arvin, MD, *Professor of Pediatrics and Microbiology & Immunology, Stanford University*

Susan Buchbinder, MD, *Director of Bridge HIV, San Francisco Department of Public Health, and Professor, UCSF*

Larry Corey, MD, *Professor and Principal Investigator, University of Washington and HIV Vaccine Trials Network, and Past President and Director, Fred Hutchinson Cancer Research Center*

Marco Cavaleri, PhD, *Head of Biological Health Threats and Vaccines Strategy, European Medicines Agency (EMA)*

Barton Haynes, MD, *Director, Human Vaccine Institute, Duke University School of Medicine*

Antonio Lanzavecchia, MD, *Director, Immune Regulation, Institute for Research in Biomedicine*

Peter Marks, MD, PhD, *Director, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA)*

John Mascola*, MD, Director, Vaccine Research Center, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Paul Offit, MD, *Professor, University of Pennsylvania, and Director, Vaccine Education Center, Children's Hospital of Philadelphia*

Michael Santos, PhD, *Associate Vice President, Science, Foundation for the NIH (FNIH)*

Brett Tolman, MA, *Strategy Manager, Deloitte*

Tonya Villafana, PhD, MPH, *Vice President, Global Franchise Head, Infection, AstraZeneca*

Tal Zaks, MD, PhD, *Chief Medical Officer, Moderna Therapeutics*

INVITED PARTICIPANTS

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Myron Cohen, MD, *Director for Global Health & Infectious Diseases, University of North Carolina (UNC) School of Medicine*

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH*

Carl Dieffenbach, PhD, *Director of the Division of AIDS, NIAID*

Peter Dull, MD, *Deputy Director, Integrated Clinical Vaccine Development, Global Health Division, Bill and Melinda Gates Foundation*

Ellen Gadbois, PhD, *Program Lead, Biosafety, Biosecurity, and Emerging Biotechnology Policy Division, Office of Science Policy, NIH*
Peter Gilbert, PhD, *Biostatistician, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center*
Jason Goldstein, PhD, *Team Leader, Immunochemistry and Cellular Development, Division of Scientific Resources, CDC*
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FNIH STAFF
Stacey Adam, PhD, *Director, Cancer, FNIH*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Mary Marovich to Everyone: 12:03 PM

Mike Cohen you are correct some AMB formulations had PEG

From Myron Cohen to Everyone: 12:04 PM

I thought so. We use that like "water"

From John Mascola to Everyone: 12:16 PM

also, immune response in NHP is better than humans, so NHP might overestimate

From Paul Offit to Everyone: 12:32 PM

Mike, I have a question

From Kathy Neuzil to Everyone: 12:32 PM

And I have a few comments

From Ann Arvin to Everyone: 12:35 PM

What will the definition of close contact be? Also presume data analysis could be based on duration of shedding above a threshold as opposed to peak?

From Larry Corey to Everyone: 12:38 PM

AS you note the strategy is to test all the proceeding and follow up samples from the initial detection so one gets the full virological spectrum of each episode of viral nasal shedding so we duration; peak titer and entire AUC so we get it all

From Tal Zaks to Everyone: 12:40 PM

A few comments from me on 50 vs. 100 data; what is the relationship between prevention of asx infection vs. what we're testing in this proposal

From Holly Janes to Everyone: 12:41 PM

A key limitation of the household transmission study that starts with enrolling index cases, and also with adding collection of household data to the ongoing Phase 3 trials, is that secondary transmission from *asymptomatic* infections will not be captured. Importantly, the proposed college study will capture secondary transmission events among ALL infections, both asymptomatic and symptomatic.

From Kathy Neuzil to Everyone: 12:45 PM

My reason for bringing it up is to think carefully. The reason attack rates are so high in colleages is because they aren't following the rules- there is a lot of mixing in many circles. this will bias toward null. We didn't see this today so be sure you are pursuing.

From (b)(6) to Everyone: 12:46 PM

Elaboration of the value of the (b)(5)
(b)(5)

(b) (5) (1) (b) (5) and (2)(b) (5). One of the principles of (b) (5) Moreover, ascertainment (b) (5) . Lastly, a particular reason (b) (5)

From Doug Lowy to Everyone: 12:46 PM

At the sub-group meeting, it was noted that measurement of viral shedding in the university student proposal would lead to various models for transmission, and that the plans for contact tracing will help to validate and refine the models. This could be relevant for future trials that could look at shedding.

From John Mascola to Everyone: 12:46 PM

do contacts need to be enrolled under IC in protocol?

From Audrey Pettifor to Everyone: 12:47 PM

@John..yes we will enroll them

Some Universities will have their own data which we hope we can also use but we want independent data that is collected by the study so that we can look systematically across contacts and schools

From Kathy Neuzil to Everyone: 12:48 PM

Why not single dose of 100 mcg with delayed second dose (end of study) rather than two 50 mcg as third arm?

From Doug Lowy to Everyone: 12:51 PM

How might the results of the proposed trial inform models for herd immunity?

From Stephanie Schrag to Everyone: 12:51 PM

Questions I have about the proposed study (from public health perspective): the limited age range could limit generalizability; could we generalize from this to the broader group of adults with mobility jn the community? Also the focus on a single product concerns me when this appears to be a huge investiment. Also to the comment now, public health would like the answer about infection and transmission asap.

From Hilary Marston to Everyone: 12:53 PM

economic impact is important; so is public health interpretation of vaccination - for example, how do we adjust quarantine guidance for vaccinated/exposed individuals? will be a common situation for HCWs

From Paula Annunziato to Everyone: 12:54 PM

The timing of results from the college student study seems critical. would we really have results by the summer?

From Holly Janes to Everyone: 12:54 PM

In response to Doug's question about modeling, the models for predicting impact of vaccines require estimates of VE against infection (both symptomatic and asymptomatic) and VE against infectiousness (both symptomatic and asymptomatic infections). As well as VE against disease. So in the absence of these estimates the models cannot adequately predict how well the vaccines will work at a population level.

From Ann Arvin to Everyone: 12:54 PM

Following on Peter's comment, opportunity to look at correlated of protection is important and relates to generalizability potentially

From Audrey Pettifor to Everyone: 12:54 PM

Its probably the only population we can do a placebo controlled trial with at this piont

From Peter Dull to Everyone: 12:55 PM

Just to flag there will be a COVAX Clinical SWAT workshop on Dec 17 (yes, during the VRBPAC/Moderna) targeting developers which makes transparent other global vaccine efforts (Oxford, inactivated Chinese/Indian vaccines, subunits) on vaccine efficacy against asymptomatic infection/transmission. These are very nascent but will also have some debate about appropriate study design with WHO representatives present.

From Audrey Pettifor to Everyone: 12:55 PM

And given high level of asymptomatic infection, low risk perception and high contacts could be really important population

From John Mascola to Everyone: 12:59 PM

I'm not sure seroconversion data in current P3 studies will answer the question. If low impact on seroconversion - we have the issue. Even if >50% impact on seroconversion, we have the seroreversion issue.

From Holly Janes to Everyone: 12:59 PM

Mentioned in Kathy's slides is an estimate we have made that the serology being done in the Phase 3 trials will miss 12-40% of asymptomatic infections, due to either lack of seroconversion or by waning antibodies in the context of the infrequent testing

From Kathy Neuzil to Everyone: 01:05 PM

I need to go.

From Carl Dieffenbach to Everyone: 01:07 PM

Doug is correct, the special population trials cost less, we need ot make sure the support is assured

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard a summary of NIH's Workshop on Post-Acute Sequelae of COVID-19, received brief updates on master protocols and agent prioritization, and discussed submitting session suggestions for IDWeek 2021.

NIH Workshop on Post-Acute Sequelae of COVID-19

Dr. Andrea Lerner presented key outcomes from a two-day workshop organized by NIAID in December to summarize existing knowledge and identify key knowledge gaps on post-acute manifestations of COVID-19. The first day of the workshop focused on 3 topics: (1) clinical observations, including a syndrome of long recovery (i.e., "Long COVID"); (2) the immune response as a pathogenic mechanism for post-acute COVID sequelae (PACS); and (3) the intersection of racial and ethnic disparities with PACS. The second day of the workshop focused on breakout sessions organized around sequelae in six areas: (1) neurological sequelae, (2) cardiovascular sequelae, (3) pulmonary sequelae, (4) renal, GI, and metabolic sequelae, (5) rheumatology and immunology sequelae, and (6) pediatric sequelae. Breakout sessions included individuals with backgrounds in clinical medicine, research, and epidemiology as well as patient partners and citizen scientists.

Key Outcomes

Clinical observations highlighted during the workshop included: (1) the severity of acute illnesses varies among patients from post-acute COVID clinics; (2) minority populations are significantly overrepresented among these patients; (3) PACS is associated with a substantial degree of mental health issues and cognitive impairment, as well as significant barriers to care (e.g., a lack of healthcare coverage and other social issues); and (4) there is a need for phenotypic characterization of PACS to create shared terminology and accepted case definitions. The World Health Organization (WHO) is developing a case report form (CRF) for PACS and has established an ICD code (U09) for "post COVID condition."

Presentations on the immune response as a pathogenic mechanism for PACS addressed (1) the potential pathogenic role and prognostic significance of autoantibodies in PACS, (2) a potential role for T-cell responses in PACS, (3) the association of multisystem inflammatory syndrome in children (MIS-C), compared to pediatric COVID, with T-cell activation phenotypes, (4) the reported sequelae of SARS and MERS, and (5) potential stem cell and preclinical animal models of PACS.

People of color experience a greater burden of disease and death from acute COVID-19 as well a greater burden of PACS. Thus, there is an urgent need to encourage inclusion of people of color in studies on PACS.

Knowledge Gaps

Breakout sessions identified both cross-cutting and domain-specific knowledge gaps. One domain-specific gap highlighted by the neurological breakout group was the apparent overlap between myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and "Long COVID," and whether the two conditions share similar disease mechanisms. Four conclusions were distilled from the cross-cutting knowledge gaps: (1) even for rare long-term complications, the magnitude of the pandemic creates a potentially significant public health impact; (2) PACS compromises a number of disease and syndromes (e.g., post-ICU syndrome and sequelae of SARS-CoV-2 infection itself); (3) because it is unclear how disparities seen in acute COVID will affect PACS, there is a need to ensure inclusion of diverse populations in studies that assess PACS; and (4) there are clear disparities in knowledge about PACS within the patient community.

The most critical knowledge gaps were also the most fundamental. PACS' basic epidemiology, natural history, and spectrum of disease needs to be described. The pathophysiology of PACS remains undefined and questions remain about which host characteristics (e.g., comorbidities, genetic factors) drive its varied manifestations. Phenotyping the disorder is critical to understanding its clinical spectrum. Key considerations to address the knowledge gaps include the need for a common vocabulary, case definitions, and data collection; the inclusion of appropriate controls and/or baseline assessments in trials for optimal understanding; the ability to leverage ongoing trials or cohorts, in particular for long-term follow-up; and the need to ensure racial, ethnic, and socioeconomic equity in the prevention and treatment of PACS.

Next steps include the dissemination of the workshop summary and organization of consensus discussions for case definitions and terminology. The workshop also fostered many new collaborations, among both researchers and citizen investigators.

Long-Term Follow-Up in Network Trials

The ACTIV-2 team expressed their interest in using the trial to study PACS, highlighting the prospective follow-up (currently up to 72 weeks) of individuals randomized to placebo or treatment early in the acute disease stage. The team emphasized that there is a window of opportunity now to standardize the collection of long-term participant outcomes data, which will enable comparisons of clinical outcomes, disease severity, and treatment across various clinical trials. Dr. Lerner agreed that such harmonization is key.

The TX-Clinical WG offered suggestions for long-term follow-up, including (1) developing an independent "rollover" protocol; (2) leveraging the NHLBI Collaborative Cohort of Cohorts for COVID-19 Research (C4R) standardized data collection; and (3) leveraging NHLBI's PETAL network, which has enrolled patients from the ORCHID trial for long-term phone follow-up. Dr. Lora Reineck indicated that PETAL investigators may be interested in working with other studies.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5).

ACTIV-1: Immunomodulators (Inpatient Phase III)

ACTIV-1 has activated 19 sites and (b) (4). The first protocol amendment, which is more operationally streamlined, was submitted to the IRB on December 3 and to the

FDA on December 4; regulatory approval is pending. A DSMB safety review is scheduled for January 7, 2021 and ACTIV-1 has submitted a statistical analysis plan to the DSMB for review.

The ACTIV-1 trial team has selected 73 US and ex-US sites and is identifying additional sites through TransCelerate and McKinsey. Regulatory submissions are in preparation across 20 sites in Latin America, including 7 sites in Argentina, 5 sites in Brazil, 6 sites in Peru, and 2 sites in Mexico. The trial team is working to identify barriers and challenges to activating these sites.

The ACTIV-1 team was interested in how other MPs deal with patients who express the desire to select their own treatment. ACTIV-1 strongly advises against this and inquired whether, and how, other studies had dealt with patient preferences. The ACTIV-2 study team similarly prohibits the guiding of treatment by patient preference. In ACTIV-1, patients are first randomized to an intervention and then randomized to active or control arms. Even without the comparisons between interventions, it will be difficult to interpret study data if patients are selecting their treatments.

ACTIV-1 reported that it has experienced contracting issues with study sites that have successfully executed contracts with other NIH institutes (e.g., NCATS, with ACTT-1). The ACTIV-1 MP subgroup will discuss ways to leverage ACTT's experience (e.g., lessons learned and best practices) with contracting issues and site activation.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has activated 80 sites and enrolled more than (b) (4). Patients are currently being enrolled to the open label study of (b) (4), but enrollment will convert to the placebo-controlled study of (b) (4) agent soon. A protocol amendment for the AstraZeneca, Synairgen, and Sagent (camostat) sub-studies was reviewed by the Clinical Science Research Consortium (CSRC) and will be submitted to FDA on December 21. Another amendment for the SAB polyclonal sub-study was reviewed at CSRC today. The ACTIV-2 team will respond to CSRC's comments and submit the amendment to FDA, and SAB's agent should onboard in late January or early February.

ACTIV-2 plans to co-enroll a separate ACTG study evaluating the impact of prior treatment with monoclonal antibodies on vaccine-induced immune responses. This protocol is in preparation. To develop a symptom endpoint for non-infused agents in ACTIV-2 phase III studies, the ACTIV-2 trial team is analyzing blinded symptom data and working with the FDA to validate a symptom diary. In addition, ACTIV-2 is following patients through a hospital endpoint to determine the predictive value of viral load on hospitalization.

The trial team continues work to activate international sites and to increase the diversity of study participants, for whom some demographic data are still missing. Focused outreach to African American participants will begin in January.

(b) (4) *Monotherapy*

ACTIV-2 plans to publish an analysis of patients treated with the 700 mg dose of (b) (4) monotherapy, with a smaller exploratory analysis of patients treated with the 7g dose. ACTIV leadership inquired whether the trial team anticipated difficulties enrolling patients (b) (4) . The team feels that in many settings, the availability of (b) (4) drug is still quite limited; however, availability could increase with the introduction of home infusions. Moreover, additional study data could result in the (b) treatment becoming standard of care, at which point the control group for ACTIV-2 would be amended.

ACTIV-3: Monoclonal Antibodies (Inpatient, Phase III)

Yesterday, ACTIV-3 enrolled its first patient into Version 2 of the protocol, which includes the (b) (4) antibody therapies. ACTIV-3 has activated 13 sites for protocol Version 2, with 61 sites registered for Version 1 at the time the trial was paused. Version 3 of the protocol was submitted to the FDA on December 14 and the ACTIV-3 subgroup is developing a late-stage protocol to conduct a factorial study with (b) (4) and (b) (4) which should be ready to submit to the FDA in January. The ACTIV-3 team's publication of its (b) (4) trial will appear in the *New England Journal of Medicine* on December 22.

ACTIV-3 also briefly described an ACTIV-related protocol, the 013 protocol for hyperimmunoglobulin study in hospitalized patients, which has (b) (4) out of its target enrollment of 500. The primary endpoint of this trial is ordinal scale at day 7.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

The ACTIV-4 pre-hospitalized protocol (4A) has activated 37 sites, including the first site in Spain, and enrolled (b) (4), with a high number of patients likely to need hospitalization due to COVID. The next step for ACTIV-4A is the addition of another study arm (e.g., P2Y12 inhibitor). The original approval was received from CONNECTS, but this arm must still receive DSMB approval.

Because ACTIV-4A has met its target enrollment (400 patients) per the initial analysis plan, the trial team is planning a DSMB assessment of interim data. ACTIV-4A is the umbrella for two additional trials (ITAC and REMAP-COVID), and data from these two trials are embedded in ACTIV-4A. A meeting to determine the process for combining these data will be completed prior to the DSMB meeting.

The ACTIV-4 in-hospital protocol (4B) has activated 7 sites and enrolled (b) (4) The trial team's primary goal is to increase the number of sites, in part with the help of CONNECTS, and to enroll as many patients as possible during the current spike in COVID-19 cases. Enrollment is expected to rise after CVS Minute Clinics begin enrolling patients, which is expected to occur in early January.

The ACTIV-4 post-hospitalized protocol (4C) has received approval from FDA and is expected to launch in early January 2021. The pace of enrollment has accelerated, and the gender, race, and age distributions of participants is reasonably uniform.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

ACTIV-5 has activated 6 sites and enrolled (b) (4). The trial team has continued to identify additional sites. Out of145 potential sites the team has identified, only 40 have expressed interest in ACTIV-5 and the team is currently working with 15 of these sites. The trial team will continue to refine activation and launch procedures in order to increase enrollment.

Agent Prioritization Update

The APC has recently completed a round of adjudication for immunomodulator and antiviral agents, finding no clear agents to move forward. For the next round of adjudication, the committee will follow up with 3 new candidate agents, including (b) (5) [redacted] and (b) (5) [redacted] Neutralizing antibody agents from Brii Bio, Sagent, Synairgen, and AstraZeneca are expected to onboard in ACTIV-2 by early January, and agents from AstraZeneca are expected to onboard with ACTIV-3 in January.

IDWeek 2021

IDWeek is a joint annual meeting of the Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, the HIV Medicine Association, the Pediatric Infectious Disease Society, and the Society of Infectious Diseases Pharmacists. IDWeek provides a forum for health professionals to collaborate, cooperate, and learn. The 2021 IDWeek will be held September 29 to October 3, 2021, and the deadline for submission of session suggestions is January 15. The WG proposed a session on *Networking Activities on COVID-19*, with speakers representing the ACTIV, RECOVERY, I-SPY-COVID, and REMAP-COVID trial networks, at minimum, because each network has a different emphasis. The format could include a panel discussion and/or breakout sessions. WG Co-Chairs Eric Hughes and Sarah Read will contact the conference organizers to discuss the proposed session suggestion.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, National Heart, Lung, and Blood Institute (NHLBI)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

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Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

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Ronald Reisler, MD, MPH, *Senior Clinical Advisor, Davis Defense Group*

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Evan Appell, *Consultant, Deloitte*

Hana Nasr, MPH, *Consultant, Deloitte*
Alex Sorosa, *Business Analyst, Deloitte*

Kelly E. Beazley, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Yves Rosenberg to Everyone: 1:30 PM

The NHLBI "cohorts of cohorts" presented here recently has standardized data collection I believe that could be shared?

Sarah Read to Everyone: 1:34 PM

Thank you, Andrea!

Eric Hughes to Everyone: 1:41 PM

Great enrollment!

Eric Hughes to Everyone: 1:48 PM

thanks Judy and ACTIV-2!

Timothy Buchman to Everyone: 1:50 PM

Well done!

Libby Higgs to Everyone: 1:51 PM

Thanks, glad to have the master protocol open again

Timothy Buchman to Everyone: 1:53 PM

For ACTIV-4 inpatient, now with this sizeable in-hospital enrollment, when is the initial analysis likely to occur?

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) discussed the possible addition of a (b)(4) factorial study for high-flow and mechanically ventilated patients in ACTIV-3, heard a presentation from NHLBI's Collaborative Cohort of Cohorts for COVID-19 Research (C4R), and reviewed updates on master protocols. The WG's next meeting will feature a summary of the recent NIAID long-term sequelae meeting and a discussion regarding use of residual samples across ACTIV trials.

(b)(4) Factorial Study in ACTIV-3

Dr. Elizabeth Higgs described the ACTIV-3 trial team's consideration of new agents in ordinal score 5 and 6 patients (those receiving high-flow oxygen or mechanical ventilation, respectively). These patients are currently excluded from receiving the agents now being tested in ACTIV-3. At the recommendation of the Agent Prioritization Subgroup, the trial team is planning to test aviptadil (VIP) in this patient population, but it is also considering a test of (b)(4) is no longer actively recommended by NIH treatment guidelines for ordinal score 5 and 6 patients, but considerable clinical equipoise remains regarding its efficacy. Although the SOLIDARITY trial showed that (b)(4) does not reduce mortality, that study's design precluded any definitive conclusions regarding impact on hospitalization, and ACTT trial results enrolled an insufficient number of ordinal 5 and 6 patients to draw conclusions on this endpoint, as well. At the same time, the impact of dexamethasone on viral replication in these patients remains unclear. For all these reasons, ACTIV-3 seeks to resolve questions about remdesivir's effectiveness.

The ACTIV-3 trial team is thus planning a potential factorial study of (b)(4) in ordinal scores 5 and 6 with potentially modified endpoints, due to the high mortality in this patient population. Some patients will be excluded from the factorial design, including some hypotensive patients taking vasopressors (who cannot receive VIP) and patients with chronic renal insufficiency (who cannot receive (b)(4)). Patients with no exclusions would be randomized to a 2X2 factorial and patients with exclusions would be randomized to one drug or the other, or their placebo arms. (b)(4) would not be study-provided but would be allowed. Dr. Higgs invited TX-Clinical WG members to provide feedback on the trial team's plan.

Clinical Equipoise

Dr. (b)(6) noted that data on (b)(4) (b)(5) Drs. (b)(6) and (b)(6) both suggested that (b)(4) (b)(5) but Dr. (b)(6) noted (b)(5) moreover, both Drs. (b)(6) and (b)(6) agreed with Dr. (b)(6) (b)(5). Dr. (b)(6) noted (b)(5)

(b) (5) [redacted]

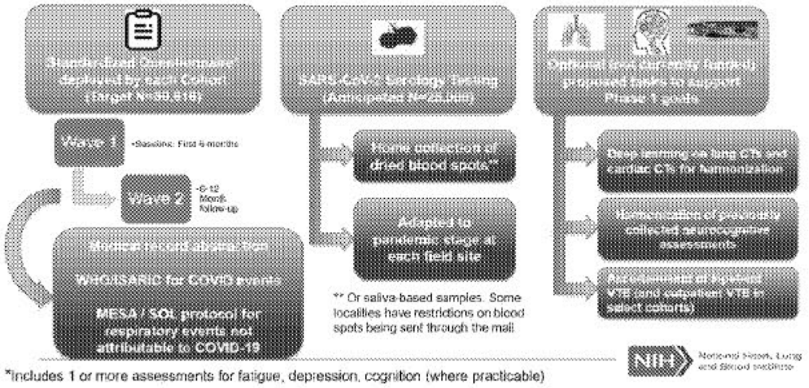
Enrollment Challenges

Dr. (b) (6) [redacted] (b) (5) [redacted] Dr. (b) (6) [redacted] agreed that enrollment (b) (5) [redacted] Dr. (b) (6) [redacted] recommended (b) (5) [redacted]

For enrollment to succeed, Dr. (b) (6) [redacted] suggested (b) (5) [redacted]. Although Dr. (b) (6) [redacted] suggested (b) (5) [redacted] Dr. (b) (6) [redacted] noted that it can be (b) (5) [redacted] un. Dr. (b) (6) [redacted] recommended (b) (5) [redacted]

Collaborative Cohort of Cohorts for COVID-19 Research

Dr. Sean Coady delivered a presentation on C4R, a collaborative of 8 NHLBI-supported population studies, 4 NHLBI-supported lung affected cohorts, and 2 NINDS stroke cohorts that was formed in response to an ROA encouraging efforts to "leverage existing infrastructure, processes and data from available cohorts or disease populations" to rapidly carry out observational studies of COVID-19. The study is racially and ethnically diverse, with 23% African American, 20% Hispanic, 5% American Indians, and 2% Asian American participants.


SARS-CoV-2 Serology Testing
Wave 1
•Sessions: First 6 months
Wave 2
•6-12 Month follow-up
Medical record abstraction
WHO/ISARIC for COVID events
MESA / SOL protocol for respiratory events not attributable to COVID-19
Home collection of dried blood spots**
Adapted to pandemic stage at each field site
Deep learning on lung CTs and cardiac CTs for harmonization
Harmonization of previously collected neurocognitive assessments

** Or saliva-based samples. Some localities have restrictions on blood spots being sent through the mail

*Includes 1 or more assessments for fatigue, depression, cognition (where practicable)

C4R's primary research questions focus on risk and resilience in individual patients and its secondary questions explore the impact of the pandemic on health trajectories in the general population. The study collects a wide range of data, including incident events, subclinical disease and functional assessments, serologic measures, and genomics. Data collection takes place through a standardized two-wave questionnaire (which extends beyond COVID ascertainment to capture fatigue, mood, depression, economic impacts, and cognitive-related measures such as brain fog); serology testing on dried blood spots or saliva; and a set of proposed follow-up tests (depicted in the chart above). C4R is also planning a case control design study to compare diagnosed COVID cases within its cohort against a control in a systematic way.

Discussion

Dr. Walter Koroshetz observed that C4R is one piece of a shift toward studies of persistent disability post-COVID, which will become increasingly important as infection rates decline. Dr. Coady noted that C4R is not adding cohorts at this time, and Dr. Adam encouraged him to contact the WG if that situation changes. Dr. Beigel noted that DAIDS would be one source of other longitudinal cohorts.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5).

ACTIV-1: Immunomodulators (Inpatient Phase III)

ACTIV-1 has activated 16 sites and (b) (4). The trial team has identified a total of 71 sites and is vetting additional sites based on lists from McKinsey, TransCelerate, and other resources; Latin American sites will open by mid-December. The trial slightly lags its enrollment targets, in large part due to challenges in site opening and an apparent mistaken exclusion of patients due to confusion regarding exclusion criteria. The current demographic distribution of the enrolled population is 63 percent White, 27 percent Black, and 9 percent other.

ACTIV-1 has submitted to FDA its first Protocol Amendment, which streamlines testing, eases burden on sites, and clarifies inclusion/exclusion criteria to increase enrollment.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has activated 78 sites and enrolled (b) (4) The trial team is now moving to open ex-U.S. sites. The team has also formed collaborations with two community groups to increase enrollment of Black patients and is exploring the possibility that the over-use of the "other" racial category has masked the actual diversity of trial participants.

ACTIV-2 sites have become adroit at infusions and additional agents are being onboarded. Brii Bio's combination Ab will be onboarded next week, at which point the open label study of the 700mg dose of (b) (4) agents will be discontinued. Brii will be followed by AstraZeneca's agent in IV and IM formulations, Synairgen's inhaled IFN beta, and camostat mesylate.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

ACTIV-3 is opening Version 2 of its protocol, which includes the Brii Bio combination therapy and GSK-Vir mAb, during the week of December 14. The addition of (b) (4) agent is planned for early January. The ACTIV-3 team's publication of its (b) (4) trial in the *New England Journal of Medicine* will appear on Dec. 22.

ACTIV-3 is interested in exploring why (b) (4) was not effective in the inpatient population. Its work on this analysis is awaiting resolution of a plan to prioritize ACTIV's biorepository of residual samples across all ACTIV trials. Dr. Adam noted that this plan will be discussed at next week's meeting of the TX-Clinical WG as well as the next Cross-ACTIV Trial Team meeting.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)
The ACTIV-4 pre-hospitalized protocol (4A) has activated 5 sites and (b) (4). The trial team expects the participation of CVS MinuteClinics to incite a rapid and substantial increase in enrolment.

The ACTIV-4 in-hospital protocol (4B) has activated 26 sites and (b) (4). The trial team's primary goal is to increase the number of sites, in part with the help of CONNECTS, and to enroll as many patients as possible during the current spike in COVID-19 cases. ACTIV-4A has also continued discussions to add a P2Y12 arm to its heparin study; that proposal is being reviewed by CONNECTS.

The ACTIV-4 post-hospitalized protocol (4C) is expected to launch within approximately one week. The pace of enrollment has accelerated and gender, racial, and age distribution of participants is fairly uniform.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)
ACTIV-5 has activated 5 sites and (b) (4). The trial team continues to work on site activation and launch procedures and on increasing enrollment.

Dr. Beigel also summarized the status of ACTT. ACTT-2's paper should appear during the next week. ACTT-3 is fully (b) (4) and should complete its final visit next week, with high-level results trial available in early to mid-January. ACTT-4's comparison of (b) (4) versus (b) (4) (both with (b) (4) in ordinal 5 and 6 patients began last week and has activated 30 sites and (b) (4).

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, National Heart, Lung, and Blood Institute (NHLBI)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Joan Butterton, MD, *VP, Clinical Research, Infectious Diseases, Merck & Co.*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

R. Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI*

Walter Koroshetz, MD, *Director, National Institute of Neurological Disorders and Stroke, NIH*

Lisa LaVange, PhD, *Professor and Associate Chair, Department of Biostatistics, UNC Chapel Hill*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, University of Pittsburgh*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

INVITED PARTICIPANTS

John Beigel, PhD, *Division of Microbiology and Infectious Diseases, NIAID, NIH*

Timothy H. Burgess, MD, MPH, *Captain, Navy*

Sean Coady, MA, *BioLINCC, RURAL Heart and Lung Study, MDAC Study, Training, NHLBI, NIH*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Joanne Lumsden, PhD, *NCATS*

Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*

Martha Petrovick, *MIT Lincoln Laboratory*

Revell Phillips, PhD, *Science and Technology Manager, Defense Threat Reduction Agency*

Dionne Price, PhD, *Office of Biostatistics of the Center for Drug Evaluation and Research, FDA*

Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*

Ronald Reisler, MD, MPH, *Senior Clinical Advisor, Davis Defense Group*

John Young, PhD, *Global Head Infectious Diseases and Vice President, Roche*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

Evan Appell, *Consultant, Deloitte*
Helen Chen, PhD, *Consultant, Deloitte*
Hana Nasr, MPH, *Consultant, Deloitte*
Alex Sorosa, *Business Analyst, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Walter Koroshetz to Everyone: 01:38 PM

Hoping to add clinical trials to test treatments in those with persistent symptoms.

From Libby Higgs to Everyone: 01:49 PM

Perhaps we need a master protocol for the Long haulers.

From Neil Aggarwal to Everyone: 02:00 PM

That is a great idea Libby. Figuring out the subphenotypes among the recovering COVID patients may be more feasible than in the acute setting, and allow for more directed treatment options.

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard status updates from its Master Protocol Subgroup and Agent Prioritization Subgroup (MPSG and APSG, respectively), as well as updates on the TX-Clinical Manuscript Subteams and Adaptive COVID-19 Treatment Trial (ACTT). The TX-Clinical WG also discussed future therapeutic strategies and priorities.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5).

ACTIV-1: Immunomodulators (Inpatient Phase III)

ACTIV-1 has activated 13 sites and (b) (4). The ACTIV-1 team has selected 46 additional sites in the U.S. and 15 in Latin America. The team has evaluated the operationalization of co-enrollment with ACTIV-4 and aims to soon submit an updated master protocol to the FDA to begin co-enrolling.

The updated protocol will also reduce the number of PK and laboratory assessments. Most ACTIV-1 agents have established safety records and thus do not require many PK assessments.

The team evaluated (b) (4) but decided not to advance the agent because of operational difficulties.

Screening procedures for ACTIV-1 have shifted to promote patient enrollment. Dr. Sam Bozzette noted that many potential ACTIV-1 patients fail screenings because of renal insufficiency, which precludes patients from receiving (b) (4). Thus, although (b) (4) is still preferred as standard of care (SOC), it will no longer be a mandatory condition of study participation. Dr. Bozzette added that the team will begin receiving screening logs from sites starting next week.

Discussion

ACTIV-3 and -4 both allow enrollment of patients with renal insufficiency (these patients do not receive (b) (4) as standard of care).

Dr. Elizabeth Higgs noted that ACTIV-3 disseminated surveys to its sites in order to identify common challenges associated with patient enrollment and recommended that ACTIV-1 perform similar surveys. Dr. Sarah Read recommended performing the survey once ACTIV-1 has activated more sites. Dr. Stacey Adam noted that the survey does ask sites about co-enrollment with other clinical trials, but does not require that they disclose who is facilitating those other trials (e.g., non-NIH entities). Participants agreed that the TX-Clinical WG would benefit from a presentation on the data collected from ACTIV-3 surveys.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has activated 62 sites and (b) (4) (177 of whom are randomized to the 700mg dose of the (b) (4)). The ACTIV-2 team is currently developing the second version of the master protocol, which includes the Brii Bio agent; subsequent versions will include camostat mesilate and agents from AstraZeneca and Synairgen.

The team has identified a discrepancy in the reported racial and ethnic distributions of its patient population; the DSMB identified approximately 40 percent of the population has Hispanic, whereas previous reports identified only 11 percent. The team is investigating the cause of this discrepancy.

In response to the (b) (4) agent's EUA approval, the team will develop a letter of amendment detailing that ACTIV-2 will complete Phase II studies of that agent and then will transition to open label administration. The (b) (4) agent will not be commercially available as a single drug at the 700mg dose and thus open label administration can aid in disseminating it. However, the next set of ACTIV-2 agents will be compared to placebo, not to the (b) (4) agent, and the (b) (4) agent will be stopped on the study once the next agent is activated.

Discussion
Dr. Judith Currier noted that the Phase II study with the 700mg dose of the (b) (4) agent will be fully analyzed, whereas the results from the 7000mg dose will result only in descriptive analyses.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

ACTIV-3 has ended its study of the (b) (4) monoclonal antibody (mAb) after the DSMB futility assessment; no significant safety signals were identified within the enrolled patient population. The ACTIV-3 team has submitted a paper to the *New England Journal of Medicine* detailing findings from the study with the (b) (4) agent.

The team is now responding to FDA comments regarding its second version of the master protocol, which will include agents from Brii Bio and GSK-Vir. The Brii Bio agent is a combination of two mAbs, both of which contain Fc modifications and thus require an extended follow-up period of 1 year (beyond the 90 day follow-up).

ACTIV-3 currently has 60 registered sites, including sites in the Denmark, Spain, and Singapore.

(b) (4) DSMB has halted enrollment of patients requiring high-flow oxygen; however, the (b) (4), is still enrolling patients.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4's in-hospital protocol has activated 12 sites and (b) (4)s. The ACTIV-4 team is in discussions with additional sites in Spain and Italy. Investigators of the in-hospital protocol have recommended adding another study arm to evaluate P2Y12 inhibitors; the NHLBI CONNECTS Network is currently evaluating this recommendation.

The pre-hospitalized protocol has activated 4 sites and (b) (4). The team has recruited a CRO to aid in site activation and hopes to expand site activation further through the use of CVS MinuteClinics.

The post-hospitalized protocol is expected to launch by end of November. The team is finalizing legal documentation and discussions with BMS and Pfizer.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

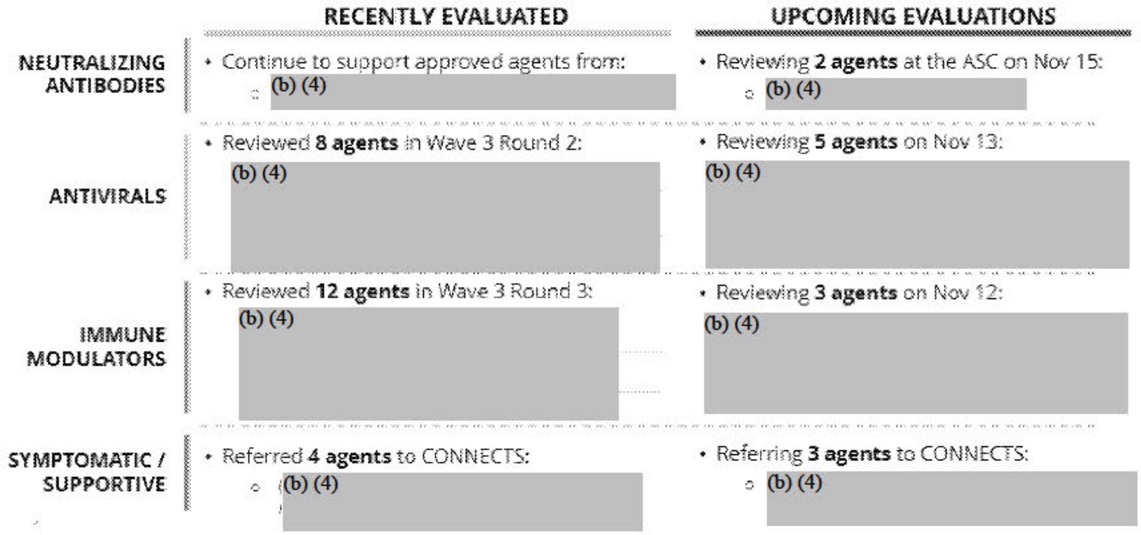
ACTIV-5 has activated 2 sites and (b) (4). The ACTIV-5 team will soon evaluate (b) (4) for inclusion in ACTIV-5.

ACTT Updates

ACTT has submitted its paper detailing ACTT-2 results to the *New England Journal of Medicine*. ACTT expects to submit to the FDA an application for ACTT-4 (comparison of (b) (4) and (b) (4) on a backbone of (b) (4) next week. ACTT-5 will involve the assessment of (b) (4).

Agent Prioritization Subgroup Updates

Dr. Adam presented updates form the APSG, summarized below:



	RECENTLY EVALUATED	UPCOMING EVALUATIONS
NEUTRALIZING ANTIBODIES	• Continue to support approved agents from: ○ (b) (4)	• Reviewing **2 agents** at the ASC on Nov 15: ○ (b) (4)
ANTIVIRALS	• Reviewed **8 agents** in Wave 3 Round 2: (b) (4)	• Reviewing **5 agents** on Nov 13: (b) (4)
IMMUNE MODULATORS	• Reviewed **12 agents** in Wave 3 Round 3: (b) (4)	• Reviewing **3 agents** on Nov 12: (b) (4)
SYMPTOMATIC / SUPPORTIVE	• Referred **4 agents** to CONNECTS: ○ (b) (4)	• Referring **3 agents** to CONNECTS: ○ (b) (4)

The APSG has requested additional PK information for the new formulation of (b) (4) (not injected) and (if the agent is approved) proposed a possible comparison to ACTIV-2's future trial of (b) (4). Most deferred agents will be revaluated upon receipt of data from ongoing small clinical trials.

Discussion

(b) (4) is currently identified as an antiviral, (b) (5) upon review by the APSG.

The APSG is currently discussing possible (b) (5) agent before it advances into ACTIV-3. Other agents soon to be included in an ACTIV trial, such as agents from (b) (4), will be advanced upon receipt of additional preclinical data.

TX-Clinical WG Manuscript Updates

The Agent Prioritization and Master Protocol Manuscript Subteams continue to draft their respective manuscripts; the Agent Prioritization Manuscript Subteam has drafted more than half of its manuscript, whereas the Master Protocol Manuscript Subteam has drafted one section thus far. Both subteams are on track to finish their first drafts before the Thanksgiving holiday and a final draft before the Christmas holidays.

Future Strategies and Priorities

Impact of Ongoing Trials and Continued Priorities

Dr. Jacqueline Kirchner inquired how the TX-Clinical WG expects its trials and activities to be impacted by additional potential EUA approvals and vaccine dissemination. Participants emphasized that these developments will not end the COVID-19 pandemic and thus continued investigation of therapeutics and vaccines is imperative to treating current and future COVID-19 patients and to prepare for future pandemics.

Dr. John Mellors noted that recent publications have detailed the potential for intra-host viral evolution and subsequent antibody-resistant viral transmission and emphasized that COVID-19 therapeutics will be needed for the foreseeable future.

Implications from Mink Colony Outbreaks

Dr. Walter Koroshetz noted that COVID-19 outbreaks have been observed in mink colonies and that these outbreaks were found to include a novel viral mutation. The TX-Clinical WG agreed that these outbreaks must be monitored to assess whether the mutations can be re-introduced to humans and cause additional harm. Dr. Adam noted that the researchers investigating the mink mutations have administered some of the antibody-based therapeutics being investigated by ACTIV and found that some may be effective, but the agents will likely be administered in combination in humans.

Considerations of Chronic Infections and Longer Follow-Up Periods

Participants discussed the significant portion of COVID-19 patients who appear to develop a chronic infection. A CDC outpatient study found that 35 percent of patients still exhibited symptoms after 2 weeks and a study in Italy found that 87 percent of patients were still symptomatic 2 months later; in comparison, flu studies typically observe that 90 percent of patients recover within 9 days.

Dr. Koroshetz noted that NIH and NHLBI are working to create plans that include longer follow-up timepoints and invited the TX-Clinical WG to refer to him any researchers that are investigating long follow-up timepoints in COVID-19 research. Dr. Yves Rosenberg will invite NHLBI colleagues to present on the NHLBI's Cohort of Cohorts during a future TX-Clinical WG meeting; the Cohort of Cohorts aims to include many long-term follow-up visits to assess the impact of COVID-19 therapeutics long after administration.

ACTIV-2 follows up with patients for 6 months and ACTIV-1 includes a 28-day follow-up visit; however, participants agreed that increasing ACTIV's follow-up requirements would help investigate chronic infections of COVID-19.

Next Steps

Dr. Eric Hughes will present data from Novartis' ongoing COVID-19 clinical trials during the next TX-Clinical WG meeting.

Appendix A: Participants List

WORKING GROUP MEMBERS

Samuel Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Timothy H. Burgess, MD, MPH, *Captain, Navy*

Joan Butterton, MD, *VP, Clinical Research, Infectious Diseases, Merck & Co.*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

R. Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI*

Walter Koroshetz, MD, *Director, National Institute of Neurological Disorders and Stroke, NIH*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, University of North Carolina*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, University of Pittsburgh*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

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INVITED PARTICIPANTS

Sylva Collins, PhD, *Director of the Office of Biostatistics, FDA*

Michelle Culp, MPH, *Office of the Director, NIH*

Ellen Gadbois, PhD, *Office of Science Policy, Office of the Director, NIH*

Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*

Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Martha Petrovick, *MIT Lincoln Laboratory*

Revell Phillips, PhD, *Science and Technology Manager, Defense Threat Reduction Agency*

Dionne Price, PhD, *Office of Biostatistics of the Center for Drug Evaluation and Research, FDA*

Felicia Qashu, PhD, *Program Officer, NIH*

Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*
Daniel Rubin, PhD, *Statistician, Center for Drug Evaluation and Research, FDA*

STAFF
Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

Evan Appell, *Consultant, Deloitte*
Helen Q. Chen, PhD, *Senior Consultant, Deloitte*
Alex Sorosa, *Business Analyst, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Libby Higgs to Everyone: 01:12 PM

(b) (4) is one of ACTIV 3's highest enrollers

From Sam's iPhone to Everyone: 01:15 PM

interesting- our PI is not at their main hospital and although she supposedly has access to patients everywhere but we wonder

From Revell Phillips to Everyone: 01:25 PM

What exactly is the standard of care in each of the ACTIV trials, and has it evolved over time?

From Libby Higgs to Everyone: 01:29 PM

For ACTIV 3 SOC includes (b) (4) provided by the study. (b) (4) is administered per the site SOC with reference to treatment guidelines in each of the countries, e.g. NIH Guidelines in the US

From Sam's iPhone to Everyone: 01:31 PM

1 allows convalescent plasma but otherwise is the same as in 3

From Timothy G. Buchman to Everyone: 01:32 PM

As an aside, it is easier to standardize certain drug/dosing than it is to standardize non-drug therapies such as respiratory support. In particular, ventilator management is very difficult to protocolize owing to unique responses.

From Libby Higgs to Everyone: 01:32 PM

Well done ACTIV 4!!

From Andrei Kindzelski to Everyone: 01:33 PM

Thank you, Libby!

From Libby Higgs to Everyone: 01:34 PM

Yes ACTIV 3 allows for enrollment in non-drug SOC protocols in the first 5 days, such as ACTIV 4, on a per protocol basis.

From Timothy G. Buchman to Everyone: 01:36 PM

At 100,000 feet, these aggregate trials seem aimed to unravel the specifics of how immune suppression actually works with the design of ACTT-4 and the range of agents in ACTIV-1

From yves rosenberg, NHLBI to Everyone: 01:44 PM

BRACE CORONA trial:https://www.escardio.org/The-ESC/Press-Office/Press-releases/LOPES

From walter koroshetz- NINDS to Everyone: 01:49 PM

Is more interest in the post covid longer term effect now

From Timothy G. Buchman to Everyone: 01:49 PM

We are, however, getting better at managing the average case.

We absolutely need better insight into longer-term consequences.

From walter koroshetz- NINDS to Everyone: 01:51 PM

think the mink issue is also a bellringer for future outbreaks in humans?

From John Mellors to Everyone: 01:52 PM

Agree

From Libby Higgs to Everyone: 01:53 PM

Only 12 cases

From yves rosenberg, NHLBI to Everyone: 01:53 PM

but we need to recruit faster now as it will become harder once a vaccine become available!

From Sam's iPhone to Everyone: 01:54 PM

12 cases of what Libby?

From Revell Phillips to Everyone: 01:55 PM

Potentially we could find treatments to help people with long term issues

From Robert Malone to Everyone: 01:55 PM

RE SARS 1 - there has been massive , sustained investment by PRC to stamp that out. So there is that.

From yves rosenberg, NHLBI to Everyone: 01:56 PM

NIH Workshop on long term consequences of COVID:

From Timothy G. Buchman to Everyone: 01:56 PM

There is a reference population of post-intensive care syndrome and post-sepsis syndrome patients. The ICU community knows them fairly well.

From Sam's iPhone to Everyone: 01:56 PM

longer term natural history studies obviously need

From yves rosenberg, NHLBI to Everyone: 01:56 PM

https://web.cvent.com/event/cf41e3b5-04e7-4e09-b25d-f33dfcd16fed/summary

From Sam's iPhone to Everyone: 01:56 PM

Needed

From Robert Malone to Everyone: 01:58 PM

Workshop would be nice, but a registry for long haulers could be nicer. I am a long hauler to some extent. That community has assembled itself via social media, and leaders are emerging. Unless USG etc gets out ahead of this, there is risk of this community starting to become active akin to the early days of LAV/HIV

There is a reference population of post-intensive care syndrome and post-sepsis syndrome patients. The ICU community knows them fairly well.

There is quite a bit of frustration building

From Libby Higgs to Everyone: 01:59 PM

Attached is a draft agenda for the NIAID workshop on post-acute COVID-19 sequelae and registration link. The agenda is not final https://cvent.me/MQAxOa

From yves rosenberg, NHLBI to Everyone: 01:59 PM

NHLBI is organizing a "cohorts of cohorts" to study this

From Robert Malone to Everyone: 01:59 PM

There are very interesting data RE Rantes levels in long haulers. Bruce Patterson.

From Timothy G. Buchman to Everyone: 02:00 PM

I have several colleagues who got COVID, were not hospitalized, but are far from normal several months after 'recovery'. Fatigue, sense of smell/taste etc. They are nevertheless back at work caring for patients.

From jacquelineki to Everyone: 02:00 PM

really helpful discussion - many thanks!

need to drop off

From Robert Malone to Everyone: 02:02 PM

Recommend that you connect with the various social media long hauler groups. They are quite large now.

From Sarah Read to Everyone: 02:02 PM

NIAID has an observational study as well: https://www.niaid.nih.gov/clinical-trials/covid-19-recon-19-study

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard a presentation from Novartis on its recent clinical trial of canakinumab, as well as status updates from its Master Protocol Subgroup (MPSG) and TX-Clinical Manuscript Subteams.

The TX-Clinical WG will not meet on November 26; the next meeting will occur on December 3.

Novartis Presentation

Dr. Stephanie Noviello presented preliminary results from Novartis's clinical trial of canakinumab. The results are currently confidential and cannot be shared in this summary; however, they will soon be published and shared more broadly.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5).

ACTIV-1: Immunomodulators (Inpatient Phase III)

ACTIV-1 has activated 14 sites and (b) (4). The current demographic distribution of the enrolled patient population is 74 percent White, 20 percent Black, and 6 percent other.

The ACTIV-1 team has selected 51 U.S. sites for participation and aims to obtain a total of 60 U.S. sites. The team has also selected 17 sites in Latin America (Argentina, Brazil, Peru, and Mexico)—with the goal to activate 30 total international sites—and continues to evaluate regulatory requirements in these countries.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has activated 68 sites and (b) (4). The enrolled patient population is now 26 percent Hispanic; the ACTIV-2 team has initiated outreach activities to increase the percentage of Black patients enrolled.

ACTIV-2 has randomized (b) (4) onto the 700mg dose of the (b) (4) agent and has stopped enrollment. The team has revised the master protocol for an open label assessment of the (b) (4) agent; this updated protocol is expected to be in effect by November 20.

The team is also finalizing the second version of the master protocol, which will include the (b) (4) agent, and has started to develop appendices for agents from (b) (4), as well as camostat mesylate.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

ACTIV-3 has completed its sub-study of the (b) (4) agent, which has received EUA for high-risk outpatients. The ACTIV-3 team submitted a publication detailing the results of its clinical trial with the (b) (4) agent and received positive feedback from the *New England Journal of Medicine.* The team expects the manuscript to be published in the next several weeks.

The team submitted the second version of its master protocol, which includes agents from Brii Bio and GSK Vir, to the FDA this week and plans to soon share it with the IRB. Studies with the Brii Bio and GSK Vir agents are expected to launch next week.

The team is currently discussing whether ACTIV-3 should activate more sites than the 60 already registered. Once the second version of the master protocol is approved, the team will reevaluate this question.

The Trial Oversight Committee has decided to wait for the ACTIV DSMB to review additional data on the (b) (4) before advancing it into ACTIV-3.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

The ACTIV-4 pre-hospitalized protocol (4A) has activated 4 sites and (b) (4). In addition to traditional site activation, the ACTIV-4A team hopes to improve patient enrollment with referrals and home-health collaborations (i.e., CVS MinuteClinics).

ACTIV-4's in-hospital protocol (4B) has activated 14 sites and (b) (4). The ACTIV-4B team is currently discussing incorporating a third arm, possibly an anti-platelet agent.

The post-hospitalized protocol (4C) is expected to launch during late November.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

ACTIV-5 has activated two sites and (b) (4). The ACTIV-5 team continues to search for new sites and is considering additional agents to integrate into its master protocol, including (b) (4) and (b) (4).

TX-Clinical WG Manuscript Updates

The Agent Prioritization Manuscript Subteam has developed content for all sections of its manuscript and is now working to refine that content; the draft will be available for TX-Clinical WG review in early December. The Master Protocol Manuscript Subteam continues to develop its content and will also likely share its drafted manuscript with the TX-Clinical WG for review at approximately the same time. Both Subteams are on track to submit their manuscripts to a journal by the end of the year.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, National Heart, Lung, and Blood Institute (NHLBI)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Joan Butterton, MD, *VP, Clinical Research, Infectious Diseases, Merck & Co.*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

R. Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI*

Walter Koroshetz, MD, *Director, National Institute of Neurological Disorders and Stroke, NIH*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, University of Pittsburgh*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

INVITED PARTICIPANTS

Timothy H. Burgess, MD, MPH, *Captain, Navy*

Michelle Culp, MPH, *Office of the Director, NIH*

Ellen Gadbois, PhD, *Office of Science Policy, Office of the Director, NIH*

Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*

Yuhan Li, MS, *Associate Director of Biostatistics, Novartis*

Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*

Hilary D. Marston, MD, MPH, *Medical Officer/Policy Advisor, NIAID, NIH*

Peter Mesenbrink, PhD, *Executive Director of Biostatistics, Novartis*

Marina Milutinovic, MD, *Global Program Head of Immunology, Hepatology, and Dermatology, Novartis*

Stephanie Noviello, MD, MPH, *Global Program Clinical Head of Immunology, Hepatology, and Dermatology, Novartis*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*
Martha Petrovick, *MIT Lincoln Laboratory*
Revell Phillips, PhD, *Science and Technology Manager, Defense Threat Reduction Agency*
Felicia Qashu, PhD, *Program Officer, NIH*
Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*
Daniel Rubin, PhD, *Statistician, Center for Drug Evaluation and Research, FDA*
Christine Sizemore, PhD, *Director, Division of International Relations, Fogarty International Center, NIH*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Evan Appell, *Consultant, Deloitte*
Alex Sorosa, *Business Analyst, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The Vaccines Working Group (WG) convened to discuss future priorities of the Vaccines WG. Topics discussed included the potential impact of (b)(5) [redacted]

Recent Accomplishments and Discussions

The Vaccine-Associated Disease Enhancement Subgroup's manuscript was accepted and published in October. Dr. Paul Offit developed a high-level summary version of the manuscript to be disseminated more broadly.

Recent topics discussed within the Vaccines WG and its Subgroup's meetings include potential pressures on regulators, implications of the first vaccine success, pediatric evaluation of vaccines, and EUA guidance documentation.

Future Vaccines WG Priorities Discussion

ACTIV Leadership requested that the Vaccines WG (b)(5) [redacted]

(b)(5) [redacted] *Placebo-Controlled Trials*

Dr. (b)(6) [redacted] (b)(5) [redacted] Dr. (b)(6) [redacted] noted (b)(5) [redacted]

Dr. (b)(6) [redacted] noted (b)(5) [redacted]

Dr. (b)(6) [redacted] noted (b)(5) [redacted] (1) (b)(5) [redacted] (2) (b)(5) [redacted]

(b) (5) [redacted]

Dr. (b) (6) (b) (5) [redacted] Dr. (b) (6) [redacted] noted (b) (5) [redacted] (1) (b) (5) [redacted] or (2) (b) (5) [redacted]]. Dr. (b) (6) [redacted] noted (b) (5) [redacted]

Dr. (b) (6) [redacted] noted (b) (5) [redacted] Drs. (b) (6) [redacted] and (b) (6) [redacted] noted (b) (5) [redacted]

(b) (5) [redacted]
Dr. (b) (6) [redacted] recommended developing (b) (5) [redacted] Dr. (b) (6) [redacted] recommended (b) (5) [redacted]

Dr. (b) (6) [redacted] recommended developing (b) (5) [redacted] Drs. (b) (6) [redacted] and (b) (6) [redacted] (b) (5) [redacted]. Dr. (b) (6) [redacted] noted (b) (5) [redacted]. Dr. (b) (6) [redacted] noted (b) (5) [redacted]

Dr. (b)(6) [redacted] noted (b)(5) [redacted] Drs. (b)(6) [redacted] and (b)(6) [redacted] (b)(5) [redacted]

Vaccine Impact on Transmission

Dr. (b)(6) [redacted] noted (b)(5) [redacted] Dr. (b)(6) [redacted] noted (b)(5) [redacted] Dr. (b)(6) [redacted] noted (b)(5) [redacted] Dr. (b)(6) [redacted] (b)(5) [redacted].

Considerations of Vaccine and Antibody-Based Therapies

Dr. (b)(6) [redacted] noted (b)(5) [redacted]

Post-Licensure Surveillance Plans

Dr. (b)(6) [redacted] (b)(5) [redacted] Dr. (b)(6) [redacted] noted (b)(5) [redacted] Dr. (b)(6) [redacted] shared that CDC (b)(5) [redacted] (1) (b)(5) [redacted] (2) (b)(5) [redacted] (3) (b)(5) [redacted]

The CDC (b)(5) [redacted]. Dr. (b)(6) [redacted] noted (b)(5) [redacted] Dr. (b)(6) [redacted] noted (b)(5) [redacted] (b)(5) [redacted] Dr. (b)(6) [redacted] shared (b)(5) [redacted]

Expanded Access Protocols

Before this meeting, Vaccines WG members proposed (b)(5) [redacted]. Dr. (b)(6) [redacted] (b)(5) [redacted] (1) (b)(5) [redacted] and (2) (b)(5) [redacted] Dr. (b)(6) [redacted] (b)(5) [redacted]; Dr. (b)(6) [redacted] (b)(5) [redacted]

(b)(5) [redacted] *Populations*

Dr. (b)(6) [redacted] (b)(5) [redacted]. Dr. (b)(6) [redacted] noted (b)(5) [redacted] Dr. (b)(6) [redacted] (b)(5) [redacted] Dr. (b)(6) [redacted] (b)(5) [redacted] Dr. (b)(6) [redacted] noted that (b)(5) [redacted]

(b)(5) [redacted] *Populations*

Another topic suggested by Vaccines WG members (b)(5) [redacted]

Dr. (b)(6) [redacted] noted (b)(5) [redacted]

Next Steps

Dr. Santos will convene a meeting with Drs. Kathrin Jansen, Lowy, Paula Annunziato, and Corey to prioritize the topics discussed during today's meeting.

Appendix A: Participants List

WORKING GROUP MEMBERS

Paula Annunziato, MD, *Vice President, Vaccine Clinical Development, Merck*

Ann Arvin, MD, *Professor of Pediatrics and Microbiology & Immunology, Stanford University*

Susan Buchbinder, MD, *Director of Bridge HIV, San Francisco Department of Public Health, and Professor, UCSF*

Larry Corey, MD, *Professor and Principal Investigator, University of Washington and HIV Vaccine Trials Network, and Past President and Director, Fred Hutchinson Cancer Research Center*

Gregory Glenn, MD, *President, Research and Development, Novavax*

Barton Haynes, MD, *Director, Human Vaccine Institute, Duke University School of Medicine*

Peter Hotez, MD, PhD, *Dean for the National School of Tropical Medicine, Baylor College of Medicine, and Director, Texas Children's Center for Vaccine Development*

Antonio Lanzavecchia, MD, *Director, Immune Regulation, Institute for Research in Biomedicine*

Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI), National Institutes of Health (NIH)*

Peter Marks, MD, PhD, *Director, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA)*

Nelson Michael, MD, PhD, *Director, Center for Infectious Disease Research, Walter Reed Army Institute of Research*

Paul Offit, MD, *Professor, University of Pennsylvania, and Director, Vaccine Education Center, Children's Hospital of Philadelphia*

Michael Santos, PhD, *Associate Vice President, Science, Foundation for the NIH (FNIH)*

Hanneke Schuitemaker, PhD, *Global Health, Viral Vaccine Discovery and Translational Medicine, Johnson & Johnson's Janssen Vaccines*

Brett Tolman, MA, *Strategy Manager, Deloitte*

Tal Zaks, MD, PhD, *Chief Medical Officer, Moderna Therapeutics*

INVITED PARTICIPANTS

Michelle Culp, BSN, MPH, *Senior Advisor, Office of Science Policy, NIH*

Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Myron Cohen, MD, *Director for Global Health & Infectious Diseases, University of North Carolina School of Medicine*

Carl Dieffenbach, PhD, *Director of the Division of AIDS, NIAID*

Ellen Gadbois, PhD, *Program Lead, Biosafety, Biosecurity, and Emerging Biotechnology Policy Division, Office of Science Policy, NIH*

Holli Hamilton, MD, MPH, *Senior Medical Officer, BARDA*

Nicole Lindsey, MS, *Epidemiologist, Centers for Disease Control and Prevention (CDC).*

Mary Marovich, MD, *Director, Vaccine Research Program, NIAID*
Stacey Martin, MSc, *Epidemiologist Team Lead, Division of Bacterial Diseases (DBD), National Center for Immunization and Respiratory Diseases (NCIRD), CDC*
Lucy McNamara, PhD, MS, *Epidemiologist, DBD, NCIRD, CDC*
Kathy Neuzil, MD, MPH, FIDSA, *Director, Center for Vaccine Development and Global Health, University of Maryland School of Medicine*
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Mike Watson, MB ChB, MRCP, AFPM, *President, Infectious Diseases, Moderna*

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Stephanie James, PhD, *Senior VP of Science, FNIH*
Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Bethany Stokes, MS*, Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard status updates from its Master Protocol Subgroup and Agent Prioritization Subgroup (MPSG and APSG, respectively), as well as updates on the TX-Clinical Manuscript Subteams.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5).

ACTIV-1: Immunomodulators (Inpatient Phase III)

ACTIV-1 has activated two sites, aims to activate an additional seven by the end of next week, and continues to identify new sites. The protocol has (b) (4) patients. The ACTIV-1 team continues to work towards facilitating co-enrollment with ACTIV-4.

Discussion

The ACTIV-1 DSMB currently allows patients to receive dexamethasone as standard of care (SOC). Participants inquired whether ACTIV-1 will address possible interaction effects between ACTIV-1 agents and (b) (4). Dr. Sam Bozzette noted that the ACTIV-1 team will try to interrogate the use of dexamethasone as a covariate. Dr. Robert Malone noted that in other clinical trials, researchers are observing a potential safety signal associated with the use of (b) (4) as SOC and increased mortality. Dr. Bozzette will share with Dr. Malone the ACTIV-1 DSMB report detailing potential dexamethasone interactions once it becomes available.

Dr. John Beigel offered to share ACTT-2 data, which sought to assess potential interaction effects between (b) (4) and (b) (4) with Dr. Malone, the ACTIV-1 team, and the ACTIV-1 DSMB. Thus far, ACTT-2 results do not raise any safety concerns related to (b) (4) interaction effects.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has (b) (4) and activated 45 sites. The ACTIV-2 trial team has begun to receive patients through the PR campaign's call center and aims to collect data tracking those results to share with the TX-Clinical WG. Enrollment of Black patients remains low and thus the PR team has initiated more targeted outreach efforts to increase this group's enrollment.

The ACTIV-2 master protocol now uses 700mg doses, instead of 7,000mg doses, and will soon restrict infusion of antibodies to high-risk patients only. The second version of this master protocol will detail that high-risk patients will be randomized to receive either the (b) (4) agent or the placebo. The ACTIV-2 trial using (b) (4) agent is transitioning to a Phase III trial, pending the outcomes of the company's application for Emergency Use Authorization (EUA).

Discussion

Dr. Judith Currier noted that the most highly enrolled sites are UCLA, University of Pittsburgh, Vanderbilt University, Ohio State, UNC Chapel Hill, and one site in Florida. Dr. Currier will share with the TX-Clinical WG a map of the currently activated ACTIV-2 sites (which is also available on the ACTIV-2 website). Dr. Currier added that the ACTIV-2 team is working to increase the number of sites within the midwestern and central United States.

Dr. Timothy G. Buchman noted that the differences in enrollment between sites largely depends on the enthusiasm of the staff at each location.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

ACTIV-3 has (b) (4) and activated 50 sites. ACTIV-3 enrollment remains paused by the DSMB, which has requested that the ACTIV-3 team present all collected data during its upcoming meeting on Monday. The ACTIV-3 team has compiled a complete dataset from all sites.

The ACTIV-3 team has developed the second version of the master protocol, which includes Brii Bio and GSK Vir; (b) (4)

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4's in-hospital protocol has (b) (4), which have thus far achieved optimal demographic distribution. The ACTIV-4 team is working to identify additional sites within the U.S. and has finalized the paperwork to soon open sites in Spain.

The pre-hospitalized protocol has (b) (4). The ACTIV-4 team expects that once additional sites are activated, enrollment for the pre-hospitalized protocol will accelerate.

The post-hospitalized protocol is ready for launch and aims to enroll patients after their involvement with the in-hospital protocol. BMS will ship supply of apixaban and placebo on November 6, which is the new target launch date for this protocol.

Discussion

Dr. Stacey Adam noted that through ACTIV-2's ongoing search to identify new sites, a number of sites were also identified for ACTIV-4's pre-hospitalized protocol.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

ACTIV-5 has activated one site and has yet to enroll any patients.

The ACTIV-5 team has launched the BET-B trial after reviewing data form Operation Warp Speed (OWS) and Roivant, which suggested that the previously observed issues with GM CSF agents were not related to safety.

Agent Prioritization Subgroup Updates

The APSG has instated new criteria that require agents to be compared within classes and shown to provide specific mechanistic or target population benefit in order to allow the APSG to more selectively advance agents into clinical trials.

During an October 20 meeting, APSG adjudicated Wave 3 Round 3 agents as either Follow-Up (i.e., agents are involved in ongoing trials and the APSG wishes to review resultant data), Defer, or Drop (summarized below).

- **Follow-Up:** (b) (4)
- **Defer:** (b) (4)
- **Drop:** (b) (4)

The APSG has also re-reviewed (b) (4) because new data have become available; it believes that this agent may benefit severely affected patients and will likely be administered in combination with (b) (4). Dr. Adam will contact Dr. Bozzette to discuss this agent further because it will likely be advanced into ACTIV-1.

The APSG will adjudicate Wave 3 Round 3 antivirals today, including (b) (4); a combination of (b) (4) a combination (b) (4) and either (b) (4); (b) (4). The APSG will also re-review (b) (4) and (b) (4); companies associated with these agents have recently supplied additional data for consideration. (Dr. Joan Butteron requested that the adjudication discussion related to (b) (4) be shared with her because it is a (b) (4) agent.)

Discussion

Participants debated whether ACTIV's agent prioritization process requires further change. Dr. Buchman asked master protocol leads if they have identified any methods to improve the process, but Dr. Bozzette noted that the process already supplies sufficient agents for ACTIV-1. Dr. Elizabeth Higgs noted that the agent prioritization process for monoclonal antibodies (mAbs) can be more difficult than for other agent classes and recommended incorporating a final step in the prioritization process during which TX-Clinical WG members review the prioritized agents. Dr. Malone noted that similar agent prioritization processes are used in DTRA trials and recommended holding a meeting between the DTRA prioritization team and the APSG to discuss possible improvements.

Participants agreed that the COVID-19 clinical trials community must begin to integrate information from all ongoing trials into a systems biology framework. Compiling this information will allow researchers to observe all pathways being targeted and the types of agents resulting in successful or non-successful clinical trials. Participants agreed that this type of framework would need to be dynamic to match the pace of COVID-19 and thus may need to be a living document that can be updated on an ongoing basis. Dr. Adam and colleagues at FNIH and Deloitte will perform a feasibility analysis of this type of project. Dr. Beigel will contact NIAID to discuss whether it has ongoing activities in this area that could be leveraged for an ACTIV project.

TX-Clinical WG Manuscript Updates

The Agent Prioritization Manuscript Subteam will convene its first meeting today and will subsequently meet weekly on Thursday afternoons. The Master Protocol Manuscript Subteam will convene its first meeting next week and alternate weekly meetings on Tuesday and Friday afternoons.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, National Heart, Lung, and Blood Institute (NHLBI)*

Samuel Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Timothy H. Burgess, MD, MPH, *Captain, Navy*

Joan Butterton, MD, *VP, Clinical Research, Infectious Diseases, Merck & Co.*

Sylva Collins, PhD, *Director of the Office of Biostatistics, FDA*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

R. Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

INVITED PARTICIPANTS

John Beigel, MD, *Associate Director for Clinical Research, Division of Microbiology & Infectious Diseases, NIAID*

Michelle Culp, MPH, *Office of the Director, NIH*

Ellen Gadbois, PhD, *Office of Science Policy, Office of the Director, NIH*

Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*

Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*

Martha Petrovick, *MIT Lincoln Laboratory*

Revell Phillips, PhD, *Science and Technology Manager, Defense Threat Reduction Agency*

Dionne Price, PhD, *Office of Biostatistics of the Center for Drug Evaluation and Research, FDA*

Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*
Ronald Reisler, MD, *Senior Clinical Advisor at David Defense Group, JPEO-CBRND-JPM CBRN Medical*
Daniel Rubin, PhD, *Statistician, Center for Drug Evaluation and Research, FDA*

STAFF
Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*
Alex Sorosa, *Business Analyst, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Eric Hughes to Everyone: 01:15PM

😄

From Eric Hughes to Everyone: 01:18PM

true Tim!

From Revell Phillips to Everyone: 01:19PM

Sounds like having committed physicians makes the biggest difference for having great sites

From Timothy G. Buchman to Everyone: 01:20PM

Honestly, it's not the physicians--it's the research coordinators and study staff.

From Timothy G. Buchman to Everyone: 01:21PM

The physicians can embrace and exhort, but it is the people on the front lines who are bringing potential subjects to screening.

From Stacey Adam to Everyone: 01:23PM

Woo Hoo! Congrats!

From Eric Hughes to Everyone: 01:23PM

Congratulations!

From Timothy G. Buchman to Everyone: 01:23PM

What wonderful success!

From Robert Malone to Everyone: 01:39PM

Strongly agree.

From Neil Aggarwal to Everyone: 01:39PM

I agree with this suggestion.

From Judith Currier to Everyone: 01:40PM

Agree with John's point- it might be a good time to take stock of what has been learned from completed trials, what is planned and how we should move forward-

From Robert Malone to Everyone: 01:40PM

Integrating standard test results across these platform trials and agents might be a good start

From Robert Malone to Everyone: 01:42PM

“This to me is what Science is about

From Robert Malone to Everyone: 01:42PM

AMEN

From Timothy G. Buchman to Everyone: 01:43PM

Concur, this is why I raised the question. I am humbled by the privilege of serving this group, but I can't escape the sense that I do not know the "big picture". I wonder if we could be more effective knowing what else is being thought, advanced, tested.

From Robert Malone to Everyone: 01:43PM

“Living entity” with AI/ML analytics

From Robert Malone to Everyone: 01:44PM

Elsivier has some really nice AIML tools that could be helpful. They have amazing data mining tools.

From Robert Malone to Everyone: 01:44PM

They spit out cascade mapping and systems analysis by drug/pathway that seems to work well

From Robert Malone to Everyone: 01:47PM

NCATS might be able to be helpful for systems biology mapping

From Eric Hughes to Everyone: 01:47PM

thanks Stacey!👍

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard status updates from its Master Protocol Subgroup and Agent Prioritization Subgroup (MPSG and APSG, respectively), as well as updates on the TX-Clinical Manuscript Subteams and new ACTIV Leadership efforts to improve master protocol site activation.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5).

ACTIV-1: Immunomodulators (Inpatient Phase III)

ACTIV-1 has activated four sites and (b)(4) (all randomized at one site). The ACTIV-1 team is meeting with each site twice per week to assess barriers to patient enrollment. The team has identified 41 sites within the U.S. for possible participation in ACTIV-1 and continues to evaluate additional sites within the U.S. and in Latin America. They have also initiated investigations into regulatory processes within Latin American countries to identify any possible complications (e.g., if samples cannot be transported out of Latin America and would require the addition of a local CRO).

The ACTIV-1 team has reviewed SOLIDARITY trial results and agreed that (b)(4) can remain within ACTIV-1's standard of care. (b)(4) is now an FDA-approved agent and thus the team must update its master protocol to reflect this change.

The ACTIV-1 team has determined that co-enrollment with ACTIV-4 must be treated as though the participant is enrolled in two separate studies (e.g., use distinct consent forms).

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has (b)(4) and activated 51 sites. Patient demographics have begun to improve, but the ACTIV-2 team continues to pursue methods to increase Black and Hispanic patient enrollment.

ACTIV-2 has transitioned to administer a 700mg dose of the (b)(4) monoclonal antibody (mAb), which will soon be advanced to a Phase III study, and will soon restrict infusions of this mAb to high-risk patients. The team has determined that there is value in continuing randomized-controlled trials of the (b)(4) even if it receives approval by the FDA for Emergency Use Authorization (EUA).

The ACTIV-2 team will develop the second version of its master protocol to include agents from (b)(4) and (b)(4) (the latter of which will be a 600mg intravenous/intramuscular dose).

Discussion

Dr. Judith Currier noted that ACTIV-2 defines high risk patients as those over the age of 60 and those under the age of 60 with comorbidities; approximately 47 percent of the current ACTIV-2 patients meet these criteria. If the (b)(4) receives an EUA, ACTIV-2 will likely continue the trial arm as an open-label clinical trial or continue the trial as is until the EUA is in full effect, because EUA dissemination of the (b) (4) agent is unlikely to occur instantaneously. The ACTIV-2 team has discussed these options with the ACTIV Trial Oversight Committee.

Dr. Currier noted that the (b) (4) mAb qualifies to advance into a Phase III study—instead of a Phase II study—because the (b) (4) study has reported additional information on the agent that can be considered. The ACTIV-2 team has shared these data with the ACTIV DSMB for review.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

The ACTIV-3 team met with the ACTIV DSMB on October 26 to discuss the possible safety signal observed in preliminary data for the (b) (4) agent. The ACTIV DSMB determined that that safety signal had attenuated and was not significant; however, it did recommend discontinuing enrollment for this agent because the results did not meet predetermined efficacy and futility thresholds.

At the time of the DSMB-recommended pause in enrollment, ACTIV-3 had (b) (4) and activated 51 sites. The ACTIV-3 team continues to work with regulatory agencies in Singapore and Denmark to open additional sites.

The ACTIV-3 team is developing the second version of its master protocol to include agents from (b) (4).

Discussion

Dr. Elizabeth Higgs noted that the TX-Clinical WG must consider whether the safety signal observed with the (b) (4) agent is a class effect; participants agreed that the TX-Clinical WG must be vigilant in reviewing data from upcoming mAb agents to assess this possibility. Dr. Higgs added that ACTIV-3 has collected baseline viral load, PK, and severe adverse events (SAEs) information, as well as data from a 5-day (inpatient) and 14-day (outpatient) follow-up to assess recovery. Dr. Currier noted that a possible class effect may cause other clinical trial researchers to avoid advancing mAbs into clinical trials, despite the likelihood that these agents will benefit hospitalized patients.

Participants also discussed why (b) (4) highest dose appeared to have the weakest effect on nasopharyngeal viral loads. They emphasized that the result may have been an artifact of small sample size or a measurement error inherent in using cycle thresholds.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4's in-hospital protocol has (b) (4) and activated 11 sites. The ACTIV-4A team is working with the NHLBI CONNECTS Network to identify a CRO to aid in ACTIV-4 site activation.

The pre-hospitalized protocol has (b) (4) and activated 7 sites. The ACTIV-4B team is pursuing opportunities to enhance site activation by integrating CVS mini-clinics.

The post-hospitalized protocol is finalized. The ACTIV-4C team is now responding to FDA comments on the ACTIV-4C post-hospitalized protocol's IND application and expects the protocol to launch by November 10, if not earlier.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

ACTIV-5 has activated one site and (b) (4). The ACTIV-5 team is experiencing delays in site activation due to slow IRB communications.

The team is working to incorporate (b) (4) into the ACTIV-5 master protocol and is waiting for additional supply and manufacturing information.

Agent Prioritization Subgroup Updates

The APSG has halted evaluation of new neutralizing antibodies (nAbs) until it can review data from the ongoing nAb trials; data will soon be requested for review.

During Wave 3 agent prioritization, the APSG has evaluated 18 antivirals and two agents--camostat mesylate and SNG001 (inhaled interferon-beta)—have been advanced to the Therapeutics-Clinical Working Group (TX-Clinical WG).

The APSG has evaluated 34 Wave 3 immune modulators and has decided to advance (b) (4) to the TX-Clinical WG (in order to gauge which master protocol would be interested in this agent).

The APSG now performs a quick triage of symptomatic support agents before transferring promising agents to the NHLBI CONNECTS Network for further review and prioritization.

Efforts to Improve ACTIV Master Protocol Site Activation

FNIH is performing outreach to additional clinical trial networks in order to mitigate site activation challenges faced by all ACTIV master protocols. Thus far, FNIH has reached out to leadership of all NIH institutes in order to assess whether associated clinical trial networks can be leveraged; it has also contacted multiple other networks, including TransCelerate, Kaiser Permanente (including both its new COVID-19 Tsar and the VP of Research), and PCORnet.

Discussion

While ACTIV Leadership is reaching out to Kaiser's newly appointed COVID-19 Czar and the VP of Research, Mr. David Wholley clarified that these leaders will conduct broad outreach to many Kaiser Permanente centers.

Dr. Yves Rosenberg inquired whether issues related to site activation (e.g., local vs. central IRB issues) are being discussed by NIH leaders. Dr. Stacey Adam noted that ACTIV facilitators are working to develop best practices documentation related to IRB-specific issues; however, some networks are not designed to include a central IRB.

TX-Clinical WG Manuscript Updates

Both the Agent Prioritization Manuscript Subteam and the Master Protocol Manuscript Subteam have established a writing team for their manuscripts and convened their first meetings. The Agent Prioritization Manuscript Subteam will meet weekly on Fridays at 4:00 pm ET and the Master Protocol Manuscript Subteam will meet on alternating Tuesdays at 4:00 pm ET or Fridays at 2:00 pm ET. Each Subteam is now soliciting volunteer writers for each section of their manuscripts. The Subteams are planning to provide first drafts to the TX-Clinical WG by late November and a final draft by late December.

Discussion

Dr. Robert Malone noted that he is helping to organize a special edition of *Frontiers in Pharmacology*, which will focus on repurposed agents, and that this edition may be a good fit for the TX-Clinical WG manuscripts.

Dr. Tim Buchman recommended considering *Clinical Care Medicine* for the TX-Clinical WG manuscripts.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, National Heart, Lung, and Blood Institute (NHLBI)*

Samuel Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Timothy H. Burgess, MD, MPH, *Captain, Navy*

Joan Butterton, MD, *VP, Clinical Research, Infectious Diseases, Merck & Co.*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI*

Walter Koroshetz, MD, *Director, National Institute of Neurological Disorders and Stroke, NIH*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*

Elliott Levy, MD, *Senior VP Global Development, Amgen; TransCelerate Board Member*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Amanda Peppercorn, MD, *Senior Medical Director, Infectious Disease, GlaxoSmithKline (GSK)*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

INVITED PARTICIPANTS

John Beigel, MD, *Associate Director for Clinical Research, Division of Microbiology & Infectious Diseases, NIAID*

Sylva Collins, PhD, *Director of the Office of Biostatistics, FDA*

Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*

Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Martha Petrovick, *MIT Lincoln Laboratory*

Dionne Price, PhD, *Office of Biostatistics of the Center for Drug Evaluation and Research, FDA*

Ronald Reisler, MD, *Senior Clinical Advisor at David Defense Group, JPEO-CBRND-JPM CBRN Medical*

Daniel Rubin, PhD, *Statistician, Center for Drug Evaluation and Research, FDA*

Christine Sizemore, PhD, *Director, Division of International Relations, Fogarty International Center, NIH*

John Young, PhD, *Global Head Infectious Diseases and Early Development, Roche*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Evan Appell, *Consultant, Deloitte*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*

Harrison Hawk, *Analyst, Deloitte*

Alex Sorosa, *Business Analyst, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Timothy G. Buchman to Everyone: 01:12 PM

Access is an important incentive to trial enrollments.

From Timothy G. Buchman to Everyone: 01:17 PM

This is an important discussion: agent or class effect?

From Walter Koroshetz to Everyone: 01:24 PM

Any ideas on why in the outpatient trial the middle dose looked better than the lower or the higher dose? Or did I get this wrong?

From Robert Malone to Everyone: 01:33 PM

Viral load analysis challenges will be a recurring problem going forward for the foreseeable future. I infer that NIH/OWS has invested in clarifying this issue?I note the BARDA BAA also has call outs on this issue

(The new BAA)

From Timothy G. Buchman to Everyone: 01:37 PM

A general question. There are many trials--some ACTIV, some others. Has progress been made on creating and populating a central data repository? So much effort is being put into gathering clinical trajectory data.

From Yves Rosenberg, NHLBI to Everyone: 01:41 PM

That's the plan at NHLBI: https://biodatacatalyst.nhlbi.nih.gov/

From Stacey Adam to Everyone: 01:42 PM

NIAID under John's supervision is also working to get something together.

From John Beigel to Everyone: 01:43 PM

ACTT data will be posted at:

https://accessclinicaldata.niaid.nih.gov/

From Robert Malone to Everyone: 01:52 PM

Have you already selected the journals?

I am helping organize a special edition of Frontiers in Pharmacology focused on repurposed drugs

I could forward you an invitation

I got clinical trial design included in scope

From Eric Hughes to Everyone: 01:57 PM

👍

From Neil Aggarwal to Everyone: 01:57 PM

Thanks all

From Timothy G. Buchman to Everyone: 01:57PM

Thanks so much!!!

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard status updates from its Master Protocol Subgroup and Agent Prioritization Subgroup (MPSG and APSG, respectively), as well as updates on the TX-Clinical Manuscript Subteams and Adaptive COVID-19 Treatment Trial (ACTT). The TX-Clinical WG also heard updates from yesterday's Executive Committee meeting, at which strategies to improve site activation were discussed.

Executive Committee Update

Drs. Eric Hughes and Sarah Read attended an ACTIV Executive Committee meeting on November 4 to continue discussing methods to improve site activation for all ACTIV master protocols. The Executive Committee's main recommendation was to form connections with other networks, such as those associated with Operation Warp Speed and TransCelerate; communications with these networks are ongoing. Dr. Francis Collins recently contacted leadership of all NIH Institutes and Centers to identify networks that can be leveraged for ACTIV master protocols; the National Cancer Institute (NCI) is currently collaborating with ACTIV-2 to leverage outpatient networks with access to sites with infusion capabilities. NIAID's Division of AIDS also reported having sites that can be made available to ACTIV master protocols.

The Executive Committee also discussed the importance of data sharing by all ongoing COVID-19 clinical trials, regardless of their affiliation with ACTIV. Only Roche has published COVID-19 data to date, but Dr. Hughes noted that many other clinical trials will soon publish COVID-19 data, as well. Dr. Read noted that the NIH Office of the Director recently met to further discuss methods to share data from ACTIV trials.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5).

ACTIV-1: Immunomodulators (Inpatient Phase III)

ACTIV-1 has activated six sites and (b) (4) (14 of these patients have been randomized at one site). The ACTIV-1 team has selected 44 additional sites in the U.S. and aims to activate approximately nine of these sites this week. The team has also selected five sites in Argentina and two in Peru and continues to survey sites in Brazil, Colombia, and Mexico. The team is also assessing how to operationalize co-enrollment with ACTIV-4.

The team is updating the master protocol to reflect the recent licensure of (b) (4). The team is also simplifying the protocol by omitting or scaling back the frequency of certain tests, including tests to assess ferritin, d-dimer, c-reactive protein, and erythrocyte sedimentation rates, in order to minimize costs. Tests used to evaluate myocarditis will not be scaled back or omitted.

Discussion

Dr. Read asked how the predicted rates of site activation are calculated because they do not appear to account for a traditional ramp-up period. Dr. Stacey Adam noted that these rates were calculated by individual master protocol trial teams to reflect ideal conditions.

Dr. Judith Currier agreed with the plan to decrease the number of required tests and noted that the need for the test must surpass the risk of staff entering the hospital room.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has activated 59 sites and (b) (4). Demographics of the enrolled patient population is improving to better reflect the predetermined optimal distribution, with 11 percent Black and 24 percent Latinx patients; the ACTIV-2 team aims to increase Black enrollment to 24 percent. The team has requested weekly demographic distribution data and will soon pursue nationwide strategies to improve enrollment of key populations. The team also continues to assess methods to improve site activation and has been calling sites frequently to discuss common challenges.

ACTIV-2 has transitioned to the 700mg dose of the (b) (4) agent (instead of the 7g dose) and 126 patients have received this dose. Upon review of the (b) (4) trial data, the ACTIV DSMB approved ACTIV-2's advancement of the (b) (4) agent into Phase III studies.

The ACTIV-2 team is developing the second version of the master protocol to include agents from (b) (4); camostat mesilate will also be included and advanced into Phase II studies.

Discussion

Dr. Adam will include slides detailing patient enrollment demographics for each master protocol in future TX-Clinical WG meeting slide decks.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

ACTIV-3 has stopped patient enrollment to and administration of the (b) (4) agent. The ACTIV-3 team has submitted to the FDA the second version of the master protocol, which includes agents from (b) (4) The team will submit a manuscript detailing preliminary results on the (b) (4) agent on November 9.

The ACTIV-3 team met with (b) (4) this week to discuss (b) (4) ongoing trial. (b) (4) has continued patient enrollment for their inpatient study, specifically enrolling patients that require no or minimal oxygen supplementation; enrollment for patients that require high flow oxygen was discontinued. (b) (4) clinical trial. FDA will soon review (b) (4) application for Emergency Use Authorization.

The team is now discussing the implications of a (b) (4)

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4's in-hospital protocol has activated 12 sites and (b) (4).

The pre-hospitalized protocol has activated four sites and (b) (4).

The post-hospitalized protocol is expected to launch on November 10, but may be delayed by one week. The team is awaiting shipment of agent and final IRB approval.

The ACTIV-4 team hopes to improve patient enrollment through partnerships with external networks and partners.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

ACTIV-5 has activated one site and (b) (4). Two of these sites are in the final stages of IRB approval. On November 3, the ACTIV-5 team met with its CRO to discuss its performance and expectations related to site activation and hopes that site activation will improve in the next several weeks.

ACTT Updates

Enrollment for ACTT-3 is expected to finish next week. The protocol for ACTT-4—which will investigate (b) (4) against (b) (4) using (b) (4) as standard of care in patients within Ordinals 5 and 6 (according to the Eight Category Ordinal Scale)—will be submitted by November 6; Dr. John Beigel expects ACTT-4 to launch during the next several weeks.

The ACTT team has responded to reviewer comments regarding its upcoming ACTT-2 publication in the New England Journal of Medicine and estimates that the publication will be released during the week of November 16.

The ACTT team has begun shipping ACTT-1 samples in order to facilitate virology studies and estimates that results will be available during late December 2020. The team will begin shipping ACTT-2 virology samples to (b) (4) and cytokine samples to (b) (4) next week.

Updates on ACTT will be added to the agenda for the ACTIV TX-Clinical WG moving forward.

Agent Prioritization Subgroup Updates

During the Executive Committee meeting on November 4, the APSG detailed the order in which nAbs will enter ACTIV master protocols (i.e., (b) (4), (b) (4) and (b) (4)). Immune modulator agents camostat mesylate and SNG001 (inhaled interferon-beta) will soon be incorporated into ACTIV-2. The APSG has proposed to advance lenzilumab and (b) (4) into ACTIV master protocols; lenzilumab will enter ACTIV-1 (b) (4) will enter ACTIV-5. The APSG will soon refer six symptomatic/supportive agents to the NHLBI CONNECTS Network.

ACTIV-3 has requested that the APSG recommend non-nAb agents for its protocol in order to develop a back-up plan in the even that nAbs exhibit a class effect.

Dr. Adam presented the timeline for agents to enter ACTIV-2 and -3, shown below:

(b) (4)

[redacted]

TX-Clinical WG Manuscript Updates

Both the Agent Prioritization and Master Protocol Development Writing Teams have met, developed strategies and outlines, and identified writers for their respective manuscripts. (Manuscript outlines and writers for each section are provided in the materials for today's meeting.) Each team's strategy is to develop manuscript sections in parallel for subsequent compilation and review. The first draft of each manuscript will be developed before the Thanksgiving holiday break and the final draft will be developed before the Christmas holiday break. The manuscript teams have decided to pursue joint publication in a high impact journal, such as the *New England Journal of Medicine* or the *Journal of the American Medical Association*.

Appendix A: Participants List

WORKING GROUP MEMBERS

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Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

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Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

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Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

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Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, University of North Carolina*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, University of Pittsburgh*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

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Michelle Culp, MPH, *Office of the Director, NIH*

Ellen Gadbois, PhD, *Office of Science Policy, Office of the Director, NIH*

Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*

Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Martha Petrovick, *MIT Lincoln Laboratory*

Revell Phillips, PhD, *Science and Technology Manager, Defense Threat Reduction Agency*

Dionne Price, PhD, *Office of Biostatistics of the Center for Drug Evaluation and Research, FDA*
Felicia Qashu, PhD, *Program Officer, NIH*
Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*
Daniel Rubin, PhD, *Statistician, Center for Drug Evaluation and Research, FDA*
John Young, PhD, *Global Head Infectious Diseases and Early Development, Roche*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*
Joseph P. Menetski, PhD, *Senior VP of Research Partnerships, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Evan Appell, *Consultant, Deloitte*
Helen Q. Chen, PhD, *Senior Consultant, Deloitte*
Alex Sorosa, *Business Analyst, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Neil Aggarwal to Everyone: 01:08 PM

That is great news!

From Timothy Buchman to Everyone: 01:08 PM

Yes!

From Revell Phillips to Everyone: 01:18 PM

Great news on the large number of sites in ACTIV 2. Hopefully the enrollment numbers will follow. Any thoughts on how to improve that?

From Timothy Buchman to Everyone: 01:25 PM

What is the current situation with (b) (4)

Interesting and thanks.

Yes.

From Timothy Buchman to Everyone: 01:39 PM

For journals, make sure the paper is edited into a single voice

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) discussed updates to the agent prioritization process, heard status updates from its Master Protocol Subgroup (MPSG), and heard updates regarding the TX-Clinical WG manuscripts.

Agent Prioritization Updates

A subset of members of the Agent Prioritization Subgroup (APSG) met to discuss methods to improve the prioritization process as the ACTIV trials approach capacity for the number of agents that can be tested in 2020. The APSG has updated the language in the automatic survey response to inform submitters that ACTIV is nearing its capacity and to advise them to anticipate a possible delayed response from the ACTIV team.

The APSG will continue to accept and review new agent submissions, but new criteria and more stringent criteria will be used in order to triage agents lacking information and advance only those with high potential. The new prioritization criteria are: (1) whether the agent shows differentiation from other agents in the same class, (2) whether the agent has strong associated preclinical or clinical data to support its readiness for clinical trials, and (3) whether the agent targets an unmet need or patient population.

These criteria will *not* apply to ACTIV-4.The APSG has suggested that the NHLBI CONNECTS Network take ownership of the agent prioritization processes for ACTIV-4 in order to streamline and reduce duplicative efforts. The APSG will continue to perform the first review of ACTIV-4 agents, but then will transition those agents to the NHLBI CONNECTS Network for further review.

Discussion

Dr. Robert Malone asked participants to share common challenges associated with patient enrollment. Participants noted the challenges of (1) identifying sites with infusion capabilities and resources, particularly when teams assess community health centers without significant clinical trial experience, (2) dealing with competition with industry clinical trials, and (3) experiencing regulatory complications with international sites.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5).

ACTIV-1: Immunomodulators (Inpatient Phase III)

ACTIV-1 launched today and patients will begin to undergo screening tomorrow. Clinical Trial Agreements (CTAs) have been finalized and executed with the three pharmaceutical companies supplying the agents and the ACTIV-1 team has received supply of both the agents and (b) (4) (the latter from Operation Warp Speed). The four agents to be tested in ACTIV-1 have been shipped to two sites and will be shipped to an additional 7 sites on October 19.

The ACTIV-1 team has identified 39 sites that have agreed to participate in ACTIV-1 and aims to secure an additional 21 sites in the U.S and 30 sites in Latin America. The team is currently developing start-up plans to activate newly obtained sites quickly and efficiently.

The ACTIV-1 and ACTIV-4 teams will meet on October 19 to further discuss how to operationalize patient co-enrollment between these two master protocols.

Discussion

Dr. Sam Bozzette noted that updates to the ACTIV-1 protocol in relation to ACTIV-4 co-enrollment are related to identifying areas to synergize across the protocols and not to combine them. He added that any complications that arise in co-enrolled sites will be transmitted to both the ACTIV-1 and -4 DSMBs. Dr. Bozzette hypothesized that many ACTIV-1 sites may be interested in co-enrollment because it allows sites to be paid twice.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has (b) (4) and activated 37 sites. It is on average enrolling approximately 1 patient per week with relatively low representation of African Americans; the ACTIV-2 team aims to mitigate these issues through PR and outreach strategies.

The ACTIV-2 team has updated the master protocol in order to administer 700mg of agent instead of 7000mg and those changes are in effect at most activated sites. It also aims to finalize an update to the master protocol to require that infused monoclonal antibodies be given only to high-risk populations.

The ACTIV-2 team will soon finalize the appendix for Brii Bio and is in discussions with AstraZeneca, SAB, and Synairgen to begin drafting appendices for their agents.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

ACTIV-3 has (b) (4) and activated 51 sites. At a routine weekly review on October 13, the ACTIV-3 DSMB determined that ACTIV-3 had crossed a specific protocol-defined safety threshold and thus recommended pausing enrollment and randomization. (This pause appears to have been leaked to the *New York Times,* which published an article that has led to multiple media inquiries to ACTIV.) The ACTIV-3 team has not yet received additional information from the DSMB regarding what specific safety issues were observed but will meet with the DSMB on October 26 to discuss whether the trials can proceed. ACTIV-3 has transmitted notices to each of its sites to stop all ongoing and upcoming patient infusions.

The ACTIV-3 team is finalizing the appendices for GSK Vir and Brii Bio and will soon begin incorporating (b) (4) into the master protocol.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4's in-hospital protocol has (b) (4). The ACTIV-4 team aims to increase site activation and patient accrual through co-enrollment with ACTIV-1.

The pre-hospital protocol has yet to enroll patients. The ACTIV-4 team has revised the master protocol to mitigate the conflicts observed between enrollment criteria and standard ER practices and those updates have been approved by the DSMB, central IRB, and the FDA. The ACTIV-4 team recently met with representatives of CVS in order to improve enrollment for the pre-hospital protocol.

The post-hospital protocol received DSMB approval and is awaiting a response from the IRB. The ACTIV-4 team anticipates launching this protocol during late-October.

Discussion

Dr. Elizabeth Higgs has contacted the FDA to obtain approval for ACTIV-3 and -4 to co-enroll patients. Once she receives a response, she will share that response with both ACTIV-1 and ACTIV-4.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

ACTIV-5 launched on October 12 and began testing its BET-A (risankizumab-rzaa) arm on October 14. The ACTIV-5 team has activated two sites and anticipates activating an additional four sites next week.

The ACTIV-5 team has paused the BET-B (lenzilumab) arm of its protocol in order to review recently released data that may suggest complications associated with all granulocyte-stimulating inhibitor compounds. The ACTIV-5 team anticipates that the BET-B arm will proceed soon.

TX-Clinical WG Manuscript Updates

Dr. Stacey Adam has received 6 to 7 volunteers for the two TX-Clinical WG manuscript subteams (i.e., Agent Prioritization and Master Protocol Development) and will soon schedule weekly subteam meetings to begin outlining and drafting.

Dr. Adam will share the eventual composed manuscripts with the TX-Clinical WG for review. The manuscripts will identify the TX-Clinical WG as an author and list all TX-Clinical WG members in the acknowledgements.

Appendix A: Participants List

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Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

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Evan Appell, *Consultant, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Libby Higgs to Everyone: 1:25 PM

YAY SAM!

From Ruxandra Draghia-Akli to Everyone: 1:25PM

Wonderful!!!!!

From Eric Hughes to Everyone: 1:26PM

CONGRATULAIONS!!

From Sam Bozzette to Everyone: 1:33PM

Thanks everyone

From Yves Rosenberg to Everyone: 1:34PM

Will we keep track of how many patients are enrolled in both trials?

From Timothy Buchman to Everyone: 1:37PM

A general question: is enrollment at established sites mirroring positivist? With the upticks globally (esp in the USA) we can hope for better enrollment.

From Sam Bozzette to Everyone: 1:37PM

good point on tracking - will do

From Timothy Buchman to Everyone: 1:43PM

Thank you, Libby. Great and thoughtful presentation.

From Sam Bozzette to Everyone: 1:46PM

I was amazed to hear the A-3 news from the BBC channel

High-Level Meeting Summary

The Preclinical Working Group (WG) discussed ongoing difficulties recruiting participants for clinical trials; acceptance of manuscripts submitted to *Cell Host & Microbe*; updates from the *In Vivo* Strategy, Data Portal Implementation, and Preclinical Network Implementation Subgroups; and scenario planning for the WG's future.

Action Items

- Dr Menetski will send the Leadership team slides to the group for their review. [done right after the meeting]
- A template with be distributed that WG members can submit their ideas for the scenario planning exercise

Clinical Trial Recruitment Difficulties

In contrast to Operation Warp Speed (OWS) vaccine clinical trials, ACTIV clinical trials have had difficulty recruiting participants; ACTIV2, for example, has recruited only 24 participants in the last month. The WG discussed potential barriers to recruitment, ranging from a lack of outreach to inform people of clinical trial eligibility to a loss of public trust in the safety and effectiveness of clinical trials in a highly politicized environment. Drs. Joseph Menetski and Rosa Maria Alvarez will schedule a meeting with members of the TX-Clinical WG to discuss strategies to increase recruitment and offer the assistance of the Preclinical WG with this effort; possible strategies raised at this meeting included notification of clinical trial eligibility following COVID-19 testing, adoption of study designs that require fewer participants to render meaningful outcomes, and financial incentives for participation.

Manuscript Acceptance

Both the Pandemic Response SOP (for *in vitro* and *in vivo* studies) and the Animal Model Landscape manuscripts have been accepted and will be published as back-to-back articles in *Cell Host & Microbe*.

Subgroup Updates

In Vivo Strategy Subgroup

OWS and ACTIV are working together to harmonize use of NHP models; formal updates on this effort will be available soon.

Best Practices for COVID-19 Research in Small Animal Models Subteam

The Subteam will meet tomorrow, September 24, for presentations on hamster and ferret models and again on October 5 for presentations on the use of hamsters for vaccine studies. Members of the Preclinical WG are welcome to attend these presentations and may contact Dr. Alvarez for more information; presentations will also be recorded and made available to those unable to attend. Insights from these sessions will be compiled into the Field Guide, which will be shared with the WG.

Data Portal Implementation Subgroup

The Subgroup is uploading a new page for an adenovirus-transduced hACE2 mouse model and working with the NIH Office of the Director and NCATS on a promotional strategy for the animal model pages.

Preclinical Network Subgroup

The Subgroup is currently performing its third wave of preclinical agent prioritization and 21 agents have been recommended for matchmaking; a detailed matchmaking status report is available in the Leadership Team slides that will be distributed by Dr. Menetski.

The WG discussed (b) (5) [redacted]

Scenario Planning

At the next meeting, the WG will carry out a scenario planning exercise in which members will discuss their vision for the future remit of the WG based on ACTIV support through the end of 2020, 2021, or 2022. Mr. Harrison Hawk and Drs. Menetski and Alvarez will distribute a forum to which WG members can submit their ideas and will compile those ideas for presentation at the next meeting.

Next Steps

Dr. Menetski will share the slides that were presented to the ACTIV Leadership Team with the WG. Drs. Menetski and Alvarez will schedule a meeting with members of the TX-Clinical WG to discuss strategies to increase clinical trial recruitment. Members of the WG who would like to attend presentations for the *Best Practices for COVID-19 Research in Small Animals* Field Guide may contact Dr. Alvarez for more information. Mr. Hawk and Drs. Menetski and Alvarez will distribute a forum to which WG members can submit their ideas for the scenario planning exercise and compile those ideas for presentation at the next meeting.

Appendix A: Participants List

WORKING GROUP MEMBERS

Peter Adams, PhD, *Health Scientist, Project Officer, BARDA*

Ralph Baric, PhD, *Dept. of Epidemiology and Dept. of Microbiology and Immunology, UNC Chapel Hill*

Kara Carter, PhD, *Executive Vice President Infectious Disease, Evotec*

Marc Charette, PhD, *Division of Cardiovascular Diseases NIH, NHLBI*

Tomas Cihlar, PhD, *VP, and Head of Virology, Gilead*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Damon Deming, PhD, *Virologist, Division of Antiviral Products, Office of New Drugs, FDA*

Michael Diamond, MD, PhD, (not in attendance) *Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University*

Ken Duncan, PhD, *Gates Foundation*

Prabhavathi Fernandes, PhD, *Retired, most recently led biotechs Cempra and DarPharma*

Josh Fessel, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Clint Florence, PhD, (not in attendance) *Program Officer, Research Resource Section, OBRR, DMID, NIAID*

Greg Gatto, PhD, *Drug Development Regulatory Project Leader, RTI*

Jay Grobler, PhD, *Director, Infectious Disease Biology, Merck*

Nancy Haigwood, PhD, *Director and Professor, Oregon National Primate Research Center, OHSU*

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Samantha Jonson, MPS, *Special Assistant to the Director, NCATS*

Cat Lutz, PhD, (not in attendance) *Senior Director, Mouse Repository & In Vivo Pharmacology, Rare and Orphan Disease Center, Jackson Laboratory*

Stephen Mason, PhD, *Associate Research Fellow, Pfizer*

Frank Nestle, MD, (not in attendance) *Global Head of Immunology Therapeutic Research Area and Chief Scientific Officer North America, Sanofi*

Liz Ottinger, PhD, *Project Manager, NCATS*

David Payne, PhD, DSc, (not in attendance) *Vice President & Head, Medicine Opportunities Research Unit, GSK*

Louise Pitt, PhD, *Director, Center for Aerobiological Sciences, USAMRIID*

Tony Punturieri, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Srinivas Rao, MBA, PhD, *Global Head Translational In Vivo Models, Sanofi*

Jay Rappaport, PhD, *Director and Chief Academic Officer, Tulane Primate Center*

John Young, PhD, *Global Head Infectious Diseases and Vice President, Roche*

INVITED PARTICIPANTS

Ellen Gadbois, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*
Sheri Hild, PhD, *Program Director for the National Primate Research Centers (NPRCs) at Office of Research Infrastructure Programs, NIH*
Isis Kanevsky, PhD, *Unit Director, Pfizer*

FNIH STAFF

Joseph P. Menetski, PhD, *Associate VP, Research Partnerships, FNIH*

Rosa Maria Alvarez, PhD, *Manager, Monitor, Deloitte*
Harrison Hawk, *Analyst, Deloitte*

Caroline Sferrazza, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Joseph Menetski to Everyone at 10:41 AM

recruitment # question

From Josh Fessel (NIH/NHLBI) to Everyone at 10:43 AM

I'm certainly far less experienced than others on this call when it comes to recruitment into clinical trials, but I'll certainly compile some thoughts on this question.

From Christine Colvis to Everyone at 10:51 AM

People probably still trust their primary care doc

From Josh Fessel (NIH/NHLBI) to Everyone at 10:52 AM

@Christine - I think some people still do, yes. Even for those people, though, contact with primary care providers is way down from the usual.

From Christine Colvis to Everyone at 10:52 AM

But they might help with the advertising of local trials

From Josh Fessel (NIH/NHLBI) to Everyone at 10:53 AM

@Christine - Yes, I think they definitely could. I think addressing this problem will take lots of effort towards engagement at all levels of the enterprise.

From Josh Fessel (NIH/NHLBI) to Everyone at 10:53 AM

And I second John's suggestion.

From Jay Rappaport to Everyone at 10:56 AM

Would be good to have a survey of patients attitudes on this

From Josh Fessel (NIH/NHLBI) to Everyone at 10:59 AM

Congratulations! Unfortunately, I need to drop off early today.

From Christine Colvis to Everyone at 11:04 AM

Directly relevant to the recruitment discussion, I just got an email from Mike Kurilla: https://journals.sagepub.com/doi/10.1177/1740774520956969

From Christine Colvis to Everyone at 11:05 AM

Although this is for gout, the point is the use of health records as a good in for recruiting for a trial

From Jay Rappaport to Everyone at 11:08 AM

Is that Colchicine? Spelling?

From Alvarez, Rosa Maria to Everyone at 11:17 AM

@Jay, There was a typo in the actual submission from the sponsor in the 'name' data category, but the other data categories had the correct spelling. We will update it in the front end of the deck. The reviewers had the full data package, so they are aware it is colchicine

From Isis Kanevsky to Everyone at 11:29 AM

Need to drop off - isis

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) received status updates from both its Master Protocol and Agent Prioritization Subgroups (MPSG and APSG, respectively), heard updates on ACTT-3, and discussed next steps for the TX-Clinical WG manuscripts.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5).

ACTIV-1: Immunomodulators (Inpatient Phase III)

The ACTIV-1 team received FDA approval today and reached agreement with the DSMB. It is also working with DCRI to open 5 to 7 additional domestic sites and with Syneos to open sites in four Latin American countries. CTSA site activation was minimally delayed by agent labelling and shipping issues that have since been resolved.

Dr. Sam Bozzette noted that FDA approval was achieved despite the agency's strong recommendation that certain adjustments be made to the IND application; biostatisticians associated with ACTIV-1 will review the FDA's recommendations for incorporation into the ACTIV-1 study design.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has (b) (4) and activated 30 sites. Its main goal in upcoming weeks is to improve site activation in order to increase patient enrollment, which may also be improved by the ongoing ACTIV-2 PR campaign. The team recently convened a meeting with the (b) (4) to discuss ways to prevent their respective trials from competing for outpatient populations.

The ACTIV-2 team continues to update the master protocol appendices to include agents from (b) (4); the Trial Oversight Committee is currently evaluating the timeline required to initiate trials with each of these agents.

Dr. Libby Higgs recently connected the ACTIV-2 team with (b) (4), which has finished Phase I studies on inhaled (b) (4) to review this agent for possible incorporation into ACTIV-2.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

ACTIV-3 has (b) (4) and activated 40 sites (including some in Denmark). The ACTIV-3 team has encountered significant challenges with international regulatory agencies that led to delays in activating international sites. ACTIV-3 sites are not activated until agent supply is received and thus certain international sites are registered but awaiting activation (e.g., Singapore sites). Thus far, patients enrolled display a nationally representative demographic distribution.

The ACTIV-3 team has developed a flipbook to support the informed consent process and enhance participant comprehension of the clinical trial process; this flipbook is available in

English and Spanish and will soon be translated into additional languages. Dr. Higgs emphasized that the flipbook is not a substitute for an informed consent form, but an additional supporting material. Dr. Higgs will share the flipbook with the TX-Clinical WG; Dr. Sarah Read suggested providing a demonstration of the flipbook during a future Cross-Trial Team meeting.

The ACTIV-3 team will share with NIH an updated appendix with information on the agents from (b) (4). The ACTIV-3 team continues to work with representatives of (b) (4) to assess whether to start its agent in Stage 1 or Stage 2; Stage 2 allows for enrollment of patients with end-stage organ dysfunction.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4's in-hospital protocol has (b) (4) as of September 30. It received DSMB approval last week and expects to receive IRB approval soon.

The pre-hospital protocol was launched during the week of September 21 but (b) (5). The original enrollment criteria included elevated d-dimer levels, but standard ER practice requires that patients with elevated d-dimer be tested for evidence of a pulmonary embolism, which usually requires hospitalization; thus, potential ACTIV-4 pre-hospitalized patients become hospitalized before they can enroll in ACTIV-4. The ACTIV-4 team has updated the enrollment criteria to state that participants' d-dimer levels will be measured only during or after the ACTIV-4 trial has occurred; the DSMB has since approved these updated enrollment criteria.

The ACTIV-4 post-hospitalization protocol has experienced significant difficulties in site activation. The ACTIV-4 team has submitted responses to DSMB comments and is collaborating with BMS and Pfizer to obtain drug and placebo supplies during October; however, both companies have estimated that these supplies will not be available until November 6.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

The ACTIV-5 team met with the FDA last week to discuss its IND application and has since resubmitted the application with an amendment to address the FDA's concerns. This updated application will also be shared with the IRB. The ACTIV-5 team anticipates that it will soon receive FDA approval and launch its master protocol next week.

ACTT-3 Update

ACTT-3 was launched on August 5 to test the use of interferon in combination with (b) (4) r against COVID-19 and has (b) (4) as of today. The ACTT-3 team met with the DSMB during September to discuss concerns related to enrolling patients at Ordinal 6 of the 8-point clinical scale; these patients require high flow oxygen or non-invasive mechanical ventilation and may experience enhanced disease upon interferon administration. The ACTT-3 team decided to omit Ordinals 6 and 7 (i.e., invasive mechanical ventilation) from the ACTT-3 study design to mitigate these concerns.

Discussion

Dr. Walter Koroshetz asked whether ACTT-3 has observed that patients with particular interferon subtypes experience more severe COVID-19 complications. Dr. John Beigel reported that certain ACTT-3 patients have SNPs or autoantibodies that enhance COVID-19 disease severity and thus ACTT-3 will employ a systems biology approach to investigate the impact of these predispositions.

Dr. Read inquired whether ACTT-3 will also test interferon in combination with dexamethasone. Dr. Beigel noted that dexamethasone will be included in ACTT-3 only if it is part of a particular clinical site's standard of care. He added that a recent study of acute respiratory distress syndrome (ARDS) found that both interferon and dexamethasone were ineffective against ARDS and dexamethasone even enhanced disease severity. The sponsor of ACTT-3's interferon agent has suggested that interferon and dexamethasone may be effective against COVID-19 individually but harmful when administered together.

Agent Prioritization Subgroup Updates

The APSG continues to seek additional information on (b) (4) and to evaluate new compounds as they are submitted for review.

The company sponsoring (b) (4) issued a press release on September 24 detailing the results of a 200-participant study, which showed that the agent significantly reduced mortality in COVID-19 patients. The APSG is following up with the company to discuss supply and is assessing which ACTIV master protocol has the capacity to initiate a trial. (b) (4) will be presented as meeting "Go" criteria during the next ACTIV Leadership Team meeting.

The APSG also convened a meeting with the ACTIV-2 team to discuss initial onboarding of SNG001, which is an inhaled interferon-beta compound.

Discussion

Dr. Beigel noted that the 200-participat (b) (4) study did not test the agent within a mechanically ventilated patient population and thus the sponsor will likely want to move to that population to assess whether late-stage patients will benefit from the drug.

TX-Clinical WG Manuscripts Update

Some members of the TX-Clinical WG have volunteered to join the TX-Clinical WG Manuscript Subteams. Subteams working on the master protocol and agent prioritization manuscripts will convene their first meetings next week.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, National Heart, Lung, and Blood Institute (NHLBI)*

Samuel Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Timothy H. Burgess, MD, MPH, *Captain, Navy*

Joan Butterton, MD, *VP, Clinical Research, Infectious Diseases, Merck & Co.*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI*

Walter Koroshetz, MD, *Director, National Institute of Neurological Disorders and Stroke, NIH*

Michael Kurilla, MD, PhD, *Director, Division of Clinical Innovation, NCATS, NIH*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

INVITED PARTICIPANTS

John Beigel, MD, *Associate Director for Clinical Research, Division of Microbiology & Infectious Diseases, NIAID*

Michelle Culp, MPH, *Office of the Director, NIH*

Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Ellen Gadbois, PhD, *Office of Science Policy, Office of the Director, NIH*

David Hone, PhD, *Chief Scientist, Vaccine and Therapeutic Division, Joint Science and Technology Office (JSTO)*

Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*

Hilary D. Marston, MD, MPH, *Medical Officer/Policy Advisor, NIAID, NIH*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Martha Petrovick, PhD, *Staff Scientist, Massachusetts Institute of Technology*

Revell Phillips, PhD, *Science and Technology Manager, Defense Threat Reduction Agency*

William G. Powderly, MD, *J. William Campbell Professor of Medicine, Director of the Institute for Clinical and Translational Sciences, Washington University in St. Louis*

Felicia Qashu, PhD, *Program Officer, NIH*

Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*

Ronald Reisler, MD, *Senior Clinical Advisor at David Defense Group, JPEO-CBRND-JPM CBRN Medical*

Thomas Stock, *Intermediate Office of the Secretary, Department of Health and Human Services*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Evan Appell, *Consultant, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Eric Hughes to Everyone: 01:15PM

Safe to proceed,

💪👍

From Libby Higgs to Everyone: 01:19PM

Congrats Sam!

From Timothy Buchman to Everyone: 01:28PM

Anything that simplifies the consent process is an important advance!

From Timothy Buchman to Everyone: 01:29PM

Have IRBs embraced "graphic novels" and flip books as enhancements or as actual alternatives to informed consent documentation?

From Timothy Buchman to Everyone: 01:30PM

"consent forms" are fairly scary...

From Ronald Reisler to Everyone: 01:41PM

Is the study allowing dexamethasone? thanks

From Timothy Buchman to Everyone: 01:44PM

For those who have asked me about changes in ICU outcomes in COVID, the link was released publicly yesterday. This single center experience seems to be fairly representative.

https://journals.lww.com/ccmjournal/Citation/9000/Declines_in_Mortality_Over_Time_for_Critically_Ill.95496.aspx

From Sarah Read to Everyone: 01:46PM

Thanks Tim!

High-Level Meeting Summary

The Preclinical Working Group (WG) discussed publication of criteria to change the SARS-CoV-2 reference strain; the long-term remit of the WG; and updates from the *In Vivo* Strategy, Data Portal Implementation, and Preclinical Network Subgroups.

Action Items

- Dr. Colvis will develop a draft preface for the criteria for adding or changing the SARS-CoV-2 reference strain to be included in the NCATS OpenData Portal
- Dr. Menetski will help the team explore ways to give a subset of WG members access to NHP and other study data; Dr. Josh Fessel will share suggestions about possible approaches.
- WG members interested in reviewing the first draft of the Small Animal Model Field Guide can contact Drs. Menetski or Alvarez to receive a copy of the draft field guide
- Any WG members active on Twitter or other social media platforms are encouraged to share the Data Portal and solicit feedback; Ms. Jonson will develop a communications toolkit to help with this.
- Agent reviewers that have been asked to sign CDAs should forward any questions about the CDA to Drs. Menetski or Alvarez.

Drs. Joseph Menetski and Rosa Alvarez will share the list of recipients of the BSL3 facilities survey for WG members to identify any other potential facilities.Criteria to Change Reference Strain

On Friday, September 11, Dr. Joseph Menetski circulated draft criteria for adding or changing the SARS-CoV-2 reference strain. Participants had no changes to the criteria, which will be posted to the NCATS Open Science Data Portal, with links in the Animal Model pages. However, they agreed that the published version should have several pieces of context, including:

1. A revised title that avoids implicit reference to the WG (i.e., the current title is “criteria to trigger discussion…”)
2. A preface describing the criteria’s purpose and naming the current virus strains. Dr. Christine Colvis volunteered to draft the preface.

Long-Term WG Remit

Access to up-to-date data Ongoing preclinical studies and clinical trials are beginning to yield results that may shape future COVID-19 preclinical research, with implications for animal models, agent prioritization decisions, and study designs (e.g., use of positive controls). Participants discussed the potential role of the Preclinical WG in assessing and operationalizing that information.

A key challenge to the WG's participation is access to proprietary information. Participants noted that drug developers regularly share data with NIH and FNIH program staff before publication, and any studies supported by NIH (e.g., COVID-19 studies prioritized for access to NPRCs) are likely expected to report to NIH on their progress. A subset of Preclinical WG members may be explicitly incorporated into these data sharing arrangements in order to receive up to date study data. As ACTIV prioritizes agents, it should also proactively incorporate data-sharing agreements into that process as a condition of sponsor participation. Agreements could stipulate that raw data will be deposited into the study-level data portal that is currently under construction, allowing anyone with portal access to retrieve results. ACTIV leadership will explore the documentation necessary to facilitate such data-sharing.

The *In Vivo* Strategy Subgroup could conduct data reviews and suggest updated recommendations. It may also engage members of the TX-Clinical WG. NHP studies have been designed to harmonize with master protocols designed by that WG, creating the opportunity for continued collaboration.

Disease Sequelae

Although COVID-19 research has to date focused on acute disease, animal models may also shed light on long-term disease sequelae. The Preclinical WG may play a role in defining the models necessary to conduct these explorations as well as supporting the prioritization of compounds that can target these disease phenotypes

While BSL-3 lab space is a limiting factor for long-term COVID-19 studies that could address disease sequelae, there are ways around this as some animals may eventually be moved out of BSL-3 spaces if testing (e.g., blood tests for antibodies) confirms they are not infectious.

Subgroup Updates

In Vivo Strategy Subgroup

Dr. Clint Florence is working to deliver various institutes (e.g., (b) (4)) a lower-passage virus that will enable recipients to propagate locally as well as viral stocks that can be used in challenge studies. To date, the only well-characterized and usable viral stock has been produced by (b) (4) in Dr. Ralph Baric's high ACE2-expressing VeroE6 cell line; NIAID is preparing to launch a hamster study comparing viral stocks with few and many polymorphisms.

The Operations Committee and Subcommittees are on track to complete their master protocol and SOPs within the next several weeks and Dr. Florence is helping arrange access to study reagents. The Subgroup is exploring funding mechanisms to support the NPRC coordinating center and specific studies; if the coordinating center task order is awarded, the unit would be established within 30 days. The Subgroup is also considering training and Quality Assurance programs that would run across the centers.

Best Practices for COVID-19 Research in Small Animal Models Subteam

The Subteam held a second productive meeting last week focused on necropsy collection guidelines, particularly in mice, and has scheduled a discussion of in-life measurements (e.g., of olfaction and taste). Members are receiving summaries of the presentations and working to revise them into the first draft of a Field Guide. In their reviews of the summaries, members should identify perceived gaps in coverage that presenters may wish to address. A full penultimate draft of the Field Guide will be circulated to all Preclinical WG members for review; members interested in reviewing an earlier version can contact Drs. Joseph Menetski or Rosa Maria Alvarez.

Data Portal Implementation Subgroup

The Subgroup is currently adding a new page to the NCATS OpenScience Data Portal for an adenovirus transduced ACE2 mouse model; after September, it will use amaintenance plan that leverages Basecamp for offline review of new literature as well as offline updates to the animal model description pages.

The data portal has received over 2000 views. The team wants to keep the momentum and continue to share the data portal via other lines of communication. Ms. Samantha Jonson is developing a communications toolkit to help WG members promote the Data Portal via social media or their institution's website.

Preclinical Network Subgroup

The Subgroup has triaged more than 30 preclinical compounds and identified several for follow-up data collection and potential matchmaking. It has also led efforts to collect additional data regarding 7 antivirals prioritized by the TX-Clinical WG (three have been connected with NIAID, three are being engaged by Drs. Menetski and Alvarez, and one has not responded to outreach). Sponsors of prioritized agents include not only drug developers but academic institutionsThe prioritization process does not favor drugs developed by pharmaceutical companies over generics or those pursued by academics. Some sponsors require confidential data agreement (CDA) that reviewers would need to sign.

The Subgroup has circulated its BSL-3 survey and received 20 completed responses. Drs. Joseph Menetski and Rosa Alvarez will share the list of recipients for WG members to identify any other potential candidates.

Next Steps

Dr. Colvis will develop a draft preface for the criteria for adding or changing the SARS-CoV-2 reference strain. Dr. Menetski will explore ways to give a subset of WG members access to NHP and other study data; Dr. Josh Fessel will share suggestions about possible approaches. Any WG members who wish to review the first draft of the Small Animal Model Field Guide can contact Drs. Menetski or Alvarez to receive a copy of the manuscript-in-progress. Any WG members active on Twitter or other social media platforms are encouraged to share the Data Portal and solicit feedback; Ms. Jonson will develop a communications toolkit to help with this. Agent reviewers asked to sign CDAs should forward any questions to Drs. Menetski or Alvarez.

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David Payne, PhD, DSc, (not in attendance) *Vice President & Head, Medicine Opportunities Research Unit, GSK*

Louise Pitt, PhD, *Director, Center for Aerobiological Sciences, USAMRIID*

Tony Punturieri, MD, PhD, (not in attendance) *Division of Lung Diseases NIH, NHLBI*

Srinivas Rao, MBA, PhD, (not in attendance) *Global Head Translational In Vivo Models, Sanofi*

Jay Rappaport, PhD, *Director and Chief Academic Officer, Tulane Primate Center*

John Young, PhD, (not in attendance) *Global Head Infectious Diseases and Vice President, Roche*

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Isis Kanevsky, PhD, *Unit Director, Pfizer*
Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

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Joseph P. Menetski, PhD, *Associate VP, Research Partnerships, FNIH*

Rosa Maria Alvarez, PhD, *Manager, Monitor, Deloitte*
Harrison Hawk, *Analyst, Deloitte*

Caroline Sferrazza, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Josh Fessel (NIH/NHLBI) to Everyone at 10:37 AM

Data sharing is something I've been doing a lot of thinking about for awhile, as have many of you I know. Joe, Rosa, and Christine, I'll share a couple of things with you via email, and you can distribute as you deem appropriate.

From Greg Gatto to Everyone at 10:52 AM

I would like to see the presentations

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) received status updates from the Master Protocol Subgroup (MPSG), including progress on ACTIV-6, and Dr. Samuel Brown presented an overview of ACTIV-3b.

ACTIV-3b Overview

Samuel Brown

ACTIV-3b (also known as TESICO) was initiated to study aviptadil—a synthetic vasoactive intestinal peptide (VIP)—in cases of acute respiratory distress syndrome (ARDS) associated with COVID-19. Dr. Samuel Brown will serve as PI for ACTIV-3b, core expertise will be provided by PETAL and CTSN, and INSIGHT SDMC will serve as the data coordination center (DCC). Enrollment will occur across PETAL, CTSN, INSIGHT, VA, and independent sites coordinated through Leidos Biomedical. In addition to providing an opportunity to bring an effective therapy to patients with COVID-ARDS, ACTIV-3b may also have substantial benefits for the treatment of ARDS more generally.

Although (b) (4) is expressed extensively throughout the body, the majority of VIP binding occurs in the lung, including in the Type 2 alveolar epithelial cells that are important in ARDS and COVID-19. Preclinical data from animal models and healthy volunteers supports the efficacy of aviptadil as an immune-modulatory, pro-surfactant, antiviral, and anti-fibrotic agent; a Calu-3 model showed that aviptadil was able to increase cell viability, decrease apoptosis, and decrease the replication of SARS-CoV-2. Data from healthy volunteers as well as in patients with COVID- and other ARDS) have shown that aviptadil may improve patient outcomes and is well-tolerated with only mild side effects in most individuals.

TESICO is a factorialized study of two agents: aviptadil (IV administration for 3 days) and (b) (4) (IV administration for up to 10 days). All enrolled patients (n=800) will have COVID-ARDS with onset within the previous 96 hours; ARDS will be defined pragmatically as the need for high flow nasal cannula (HFNC), non-invasive ventilation (NIV), or invasive mechanical ventilation (IMV). Most patients will undergo simultaneous randomization to aviptadil and (b) (4) versus their respective placebos, although non-overlapping exclusion criteria (i.e., contraindications to either drug or previous use of (b) (4) will require some patients to enter the study without the other factor. TESICO will employ a vanguard cohort approach given the critical nature of the patient population, with 20 vanguard patients in each study arm.

The primary endpoint is a hierarchical composite based on recovery assessed at 90 days after randomization. For patients who have recovered on day 90, the number of days to recovery will be measured. Patients who have not recovered on day 90 will be sorted into 3 ordinal categories: out of hospital but not recovered, hospitalized, or dead.

ACTIV-3b has received approval from the ACTIV-3 DSMB and the IND is currently under review at the FDA; coordination with the European Medicines Agency has also begun and will progress following FDA approval of the IND. ACTIV-3b anticipates first patient/first visit in early March for the vanguard cohort with expansion to the full cohort approximately 3 weeks later.

Discussion

Standard of Care and Other Agents

The administration of (b) (4) [redacted] has decreased in the COVID-ARDS population. Dexamethasone, however, is considered standard of care, and although it will not be provided by the study, Dr. Brown expects that most patients in ACTIV-3b will be taking a glucocorticoid. Based on official standard of care guidelines, the administration of anticoagulants is presently left to clinical discretion; however, Dr. Brown anticipates that ACTIV-3b may eventually recommend against the administration of anticoagulants in light of recent data from ACTIV-4.

Dose-Response Data for Aviptadil

The aviptadil dose that will be administered in TESICO has been shown to reach 10 nanomolar in alveolar epithelial cells—approximately 3- to 4-fold higher than the concentration of VIP observed in a previous study of COVID-ARDS. The planned dose is not the maximum tolerated dose as defined by healthy volunteer experiments, which is approximately 4-fold higher.

Definition of ARDS

The inclusion criteria require that patients be supported by HFNC, NIV, or IMV for acute hypoxemic respiratory failure caused by COVID-19 associated pneumonia. Unpublished data from (b) (4) [redacted].

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5/-6):

ACTIV-1: Immunomodulators (Inpatient Phase III)

ACTIV-1 has activated 38 sites, including five satellite sites, and randomized 375 participants as of February 17. The demographic distribution of participants continues to be balanced. The team has selected 86 additional sites (62 U.S. and 24 ex-U.S.) for study participation. Site activation, while slow, is anticipated in Argentina, Brazil, and Peru during the week of February 21, and 15-20 Latin American sites are expected to open in the next 4 weeks. The ACTIV-1 team plans to respond to FDA comments on the protocol amendment and Statistical Analysis Plan (SAP) by February 26.

Co-enrollment with ACTIV-4a is still on hold. The team also continues to evaluate challenges regarding the Cenicriviroc (CVC) sub-study that may impact overall study enrollment.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has activated 107 sites, although not all sites are enrolling at this time. Since January 5, (b) (4) [redacted] from 71 sites have been enrolled to the (b) (4) [redacted] agent as of February 17. Version 3.0 of the protocol has begun enrollment and patients have been randomized to 3 of the 4 agents (all except for the (b) (4) [redacted] infusion). Version 4.0 of the protocol, which includes the polyclonal antibody from SAB, will be submitted to the FDA by February 19. The team is also working with (b) (4) and RU-BMS to incorporate their agents into Version 5.0.

The ACTIV-2 team met with the FDA on February 11 to discuss a proposed symptomatic endpoint for future Versions of the protocol. The FDA indicated that a symptom-based endpoint is insufficient to justify an emergency use authorization (EUA); such an endpoint does not justify the safety risk often involved in an EUA. The team is also working to assess the cause of lengthy transition times between protocol versions and continues its barbershop initiative to improve enrollment of African American participants.

Discussion

The ACTIV-2 team argued that a symptomatic endpoint may be justifiable for an EUA because no oral or non-IV agents exist for outpatient treatment of COVID-19 and because such agents have the potential to reduce transmission of SARS-CoV-2; however, they acknowledged current data are insufficient to robustly support the latter claim. Dr. Currier noted that full approvals may not require much more time than EUAs, given the relative availability of low-risk participants for outpatient trials. Dr. Currier added that the ACTIV-2 team is currently working with the FDA and (b) (4) on a possible virologic endpoint.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

ACTIV-3 has activated 59 sites as of February 17 and has opened 40 sites on Version 3.0 of the protocol. As of February 18, (b) (4).

The ACTIV-3 team continues to work to incorporate the (b) (4) agent into the master protocol, although adequate product will not be available until mid-April. A CDA is now in place for the Pfizer protease inhibitor that was approved to enter ACTIV-3. The DSMB will meet on March 1 to conduct a futility analysis of the (b) (4) (Dr. Libby Higgs noted that the ACTIV-3 team employs a pharmacovigilance approach to its studies, which entails a weekly DSMB review of safety issues for each arm).

Site activation has been slow, particularly for ex-U.S. sites. Participants have been enrolled in Poland and Denmark; sites are open (but not yet enrolling) in Singapore and Switzerland; and a site has been registered in India.

The ACTIV-3 team broke the blind on the first trial with the (b) (4) agent and hopes to share data with the WG in the near future regarding the potential prognostic ability of plasma antigen levels.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4A (hospitalized) remains paused as the arms for the next trial are finalized. Current plans call for hospitalized patients with mild COVID-19 to receive a therapeutic dose of anticoagulants with or without P2Y12 inhibitors, and for patients with severe COVID-19 to receive the ICU-level standard of care, including prophylactic anticoagulants with or without P2Y12 inhibitors.

ACTIV-4B (pre-hospitalized) has begun a pilot program to enroll patients through CVS and has (b) (4) via this pathway to date. The ACTIV-4 team is awaiting DSMB feedback on Version 5.6 of the protocol, which primarily addresses coordination with CVS and Covance labs.

ACTIV-4C (post-hospitalization) has (b) (4) and the team is working to rapidly increase the number of active sites, including by transitioning hospitalized patients to ACTIV-4C as they convalesce.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

ACTIV-5 has activated 17 sites and (b) (4). BET-B (Lenzilumab) is on a temporary hold following notice from the contract manufacturer that environmental samples from its production line recently failed a sterility test.

ACTIV-6: Pragmatic Platform Trial (Outpatient)

ACTIV-6 is an outpatient, pragmatic platform trial to evaluate generic and widely available drugs for COVID-19 treatment. The first drug tested in ACTIV-6 will be ivermectin, which will be supplied by Ingenus along with corresponding placebo. The ACTIV-6 team is currently identifying endpoints, which will likely be a hybrid of hard and symptomatic endpoints. PCORnet will be the lead network, and other networks (e.g., NHLBI/SIREN) are expected to collaborate. The team has identified 80 domestic sites to start the trial. The team has also developed a draft trial synopsis and aligned on a governance structure that includes the ACTIV-2/3 Trial Oversight Committee and leveraging the PCORnet HERO-HCQ DSMB.

ACTIV-6 has not yet been publicly announced.

Next Steps

Dr. Beigel will present results from ACTT-3 at the next meeting; Dr. Beigel noted that ACTT-4 has enrolled (b) (4) and anticipates full enrollment by mid-April.

Appendix A: Participants List

WORKING GROUP MEMBERS

Samuel Bozzette, MD, PhD, *Chief Medical Officer, NCATS*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority*

Captain Timothy H. Burgess, MD, MPH, *Director, Infectious Diseases Clinical Research Program, Uniformed Services University of the Health Sciences*

Joan Butterton, MD, *VP, Clinical Research, Infectious Diseases, Merck*

Judith Currier, MD, *Professor of Medicine, UCLA Division of Infectious Diseases*

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Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, NIAID*

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Walter Koroshetz, MD, *Director, NINDS*

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John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, University of Pittsburgh*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, NIAID*

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Peter Wung, MD, *Associate VP, Global OMD Lead, Immuno-Inflammation, Sanofi*

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Ellen Gadbois, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*

Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*

Joanne Lumsden, PhD, *Senior Scientific Program Manager, Drug Development Partnership Programs, NCATS*

Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Martha Petrovick, PhD, *MIT Lincoln Laboratory*

Revell Phillips, PhD, *Science and Technology Manager, DTRA*

Ronald Reisler, MD, MPH, *Senior Clinical Advisor, Davis Defense Group*
Daniel Rubin, PhD, *Statistician, Center for Drug Evaluation and Research, FDA*
Christine Sizemore, PhD, *Director, Division of International Relations, Fogarty International Center, NIH*

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Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Evan Appell, *Consultant, Deloitte*
Helen Chen, PhD, *Consultant, Deloitte*
Hana Nasr, *Consultant, Deloitte*
Alex Sorosa, *Business Analyst, Deloitte*

Caroline Sferrazza, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Libby Higgs to Everyone: 1:04 PM

Sam may be coming over from an FDA meeting

Samuel Brown to Everyone: 1:04 PM

Yes, just got here. thanks

Revell Phillips (DTRA) to Everyone: 1:14 PM

So everyone isn't getting (b)(4) How about (b)(4) ?

Nice design

Walter Koroshetz to Everyone: 1:20 PM

Anything known about dose/response? Giving maximal tolerated?

Libby Higgs to Everyone: 1:20 PM

No it is primarily a factorial design so we will be able to assess (b)(4) efficacy in this population as well.

Revell Phillips (DTRA) to Everyone: 1:22 PM

Anticoagulants also

Ronald Reisler MD MPH to Everyone: 1:22 PM

How are you defining ARDS? thanks

Libby Higgs to Everyone: 1:27 PM

If a a given patient has a contraindication to one of the two drugs, e.g (b)(4) or (b)(4) they be randomized to just the (b)(4) arm or the (b)(4) , e.g. to the one they are able to receive

It would be helpful to have a COVID-19 ARDS definition ti harmonize across trials

Revell Phillips (DTRA) to Everyone: 1:28 PM

Thank You!

Eric Hughes to Everyone: 1:28 PM

Thanks Sam! Super helpful

Eric Hughes to Everyone: 1:49 PM

Libby - looking forward to hearing about the data! Thanks!

Libby Higgs to Everyone: 1:52 PM

Jaquie, We are using the (b) (4) so requires a very small sample.

Jacqueline Kirchner to Everyone: 1:59 PM

thank you, Libby! Given the sensitivity, can you comment on how whether the data indicate a higher viral load in late disease than has been observed by other methods?

Walter Koroshetz to Everyone: 2:00 PM

announcement of the post acute sequelae of COVID research https://covid19.nih.gov/sites/default/files/2021-02/PASC-Pre-Notice.pdf

Timothy G. Buchman to Everyone: 2:00 PM

Are you imagining at least some minimum effect or, reciprocally, some maximum trial size for ACTIV-6?

Timothy G. Buchman to Everyone: 2:01 PM

Is the Ivermectin selection--or ACTIV-6 existence--public information?

Libby Higgs to Everyone: 2:01 PM

Jaqueline, not sure how it will correlate. ACTT 1 is planning on using this platform and they also collected virus. So we might be able to get a correlation. For ACTIV 3 we have internal data to the study and can look across patient in the ordinal scale.

Timothy G. Buchman to Everyone: 2:04 PM

Copy that.

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High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard a presentation by Dr. John Beigel regarding the preliminary results of the Adaptive COVID-19 Treatment Trial 2 (ACTT-2) of (b) (4) [redacted].

ACTT-2 Trial Preliminary Results

Dr. John Beigel, Division of Microbiology & Infectious Diseases, NIAID

Dr. John Beigel presented the preliminary results of the ACTT-2 trial of baricitinib, noting that database lock was completed on September 10 and these top-line results leave a significant amount of data analyses still to come. The full results will be summarized within a manuscript publication during the next several weeks.

ACTT-2 was facilitated through extensive collaborations (e.g., with IDCRC, IDCRP, and (b) (4) [redacted] and partnerships with many sites in the United States and other countries (i.e., Denmark, Japan, South Korea, Mexico, Singapore, Spain, and the UK).

Study Design

The ACTT-2 target population is hospitalized adults with SARS-CoV-2 with evidence of lower respiratory tract disease. Subjects were randomized to receive either (b) (4) [redacted] and (b) (4) [redacted] or placebo and remdesivir; baricitinib and the placebo were administered for 14 days, whereas remdesivir was administered for 5 to 10 days (depending on the participant's indication).

ACTT-2 activated 67 sites—most of which were leveraged from the ACTT-1 network—and enrolled 1,033 participants in 54 days (from May to July). Most sites (b) (4) [redacted] participants per day during this time.

Ordinal Score

The ACTT-2 team used the ACTT-1 ordinal score system (shown below) to categorize a participant's baseline level of hospitalization and oxygen administration requirements.

- Ordinal Score 1: Not hospitalized, no limitations on activities
- Ordinal Score 2: Not hospitalized, limitation on activities and/or requiring home oxygen
- Ordinal Score 3: Hospitalized, not requiring supplemental oxygen, no longer requiring ongoing medical care
- Ordinal Score 4: Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care
- Ordinal Score 5: Hospitalized, requiring supplemental oxygen

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- Ordinal Score 6: Hospitalized, on non-invasive ventilation (XXX) or high-flow oxygen
- Ordinal Score 7: Hospitalized, on mechanical ventilation or extracorporeal oxygenation
- Ordinal Score 8: Death

Primary Endpoint

The primary endpoint was time to recovery measured by ordinal score. Ordinal Scores 1 to 3 signify recovered status. Preliminary data showed that the median time to recovery was 7 days in (b) (4) arm compared to 8 days in placebo arm, with a recovery rate ratio of 1.16 and a p-value of 0.03.

Ordinal 6 showed the highest recovery rate ratio (1.52), whereas Ordinal 4 showed the lowest (0.88). Ordinals 5 and 6 also had significantly higher proportions of recovered participants in the (b) (4) compared to the placebo group, while in Ordinals 4 and 7, the placebo and (b) (4) groups had relatively similar recovery rates.

Secondary Endpoint

The secondary endpoint for ACTT-2 is ordinal score at day 15. Ordinal 6 displayed the highest odds ratio, indicating participants with a baseline ordinal score of 6 were most likely to improve to a lower (improved) ordinal score within 15 days. Ordinal 4 displayed the lowest odds ratio.

Dr. Beigel presented shifted bar plots for each ordinal score, which can illustrate whether patients progressed to higher or lower ordinal scores after 15 days. For Ordinal 4, participants either remained at Ordinal 4 or improved. Those with a baseline Ordinal 5 score tended to recover and reach lower ordinal scores after Day 15, but a subset of participants worsened. Data for Ordinal 6 showed that most participants are recovering, although a subset of patients worsened. Most Ordinal 7 participants remained in Ordinal 7 until Day 15. In ordinal 5-7, in the (b) (4) arm there were fewer participants with worsened clinical status

Mortality

ACTT-1 also collected data on mortality, which revealed no deaths within Ordinal 4. Ordinal 6 had the lowest hazards ration (0.4 at Day 28) with (b) (4) Dr. Beigel noted that separation of KM mortality curves in Ordinal 6 appeared to plateau near Day 16, suggested that longer dosing may be helpful.

Comparison to RECOVERY Trial

The RECOVERY trial is a large UK-based study that assessed the impact of dexamethasone, a corticosteroid on COVID-19 with a 14 day follow-up timepoint. Approximately 20 percent of ACTT-2 patients received some form of corticosteroid during their treatment, which may affect comparisons between the RECOVERY and ACTT-2 trials; however, efficacy and safety data to evaluate steroid impact within ACTT-2 are not yet available.

The RECOVERY trial's study design differs from that of ACTT-2 in several ways: the Recovery trial did not blind its participants; participants were sorted by level of oxygen provided (i.e., no oxygen, oxygen only, and invasive mechanical ventilation); fewer exclusion criteria were used to

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select participants (potentially allowing sicker patients); and the treatment was not tested in combination with (b) (4).

Overall mortality rate at day 28 was 5.1 for (b) (4) (7.8 for the placebo), whereas in RECOVERY (b) (4)'s mortality rate was 22.9, compared to 25.7 in the placebo group. Outcomes appear most favorable for Ordinal Scores 5 and 6 within the ACTT-2 study and in the participants provided invasive mechanical ventilation in the RECOVERY study.

Additional safety data, including data on serious adverse events, will be available soon. The September 9 Data Safety Monitoring Board (DSMB) report's preliminary safety information suggested that deaths due to infection were similarly prevalent within the baricitinib and placebo groups and the (b) (4) group incurred fewer deaths due to respiratory conditions than the placebo group.

Impact on ACTIV-5The ACTT-2 trial team reviewed its ACTT-1 and -2 data with ACTIV-5 investigators. The decision was made to not enroll participants from Ordinal 4 because these patients tend to recover best on (b) (4) alone and appear to worsen on both dexamethasone and (b) (4)

Comparison of ACTT-1 and ACTT-2 Results

Investigators observed a significant increase in survival and decrease in mortality within the ACTT-2 (b) (4) control group compared to the ACTT-1 remdesivir control group, suggesting that the standard of care has improved since ACTT-1. Participants who received (b) (4) displayed the lowest mortality rates and highest survival rates. There was clear improvement in KM curves with each study and each arm within Ordinals 4- 6. Ordinal 7 was not significantly improved across the 4 arms.

Press Release

Eli Lilly issued a press release on baricitinib on September 14. Eli Lilly also recently requested a meeting with the FDA to discuss possible Emergency Use Authorization (EUA) implementation.

Next Steps

The ACTT-2 team will continue to evaluate the ACTT-2 data; however, the data thus far suggest a possible benefit to patients who are hospitalized and require both high- and low-flow oxygen, as well as patients on mechanical ventilation. Comparisons of ACTT-2 and RECOVERY trials have not identified whether (b) (4) or (b) (4) is a better strategy against COVID-19, perhaps in part due to the innate study design differences, including different patient populations; however, comparisons thus far may suggest that (b) (4) is more beneficial for high- and low-flow oxygen patients, whereas dexamethasone may be better for mechanically ventilated patients.

The next logical step for ACTT Network would be to facilitate a head-to-head trial with (b) (4) versus (b) (4)e; however, Dr. Beigel noted that such a trial may not be feasible given dexamethasone's established use in clinics. He noted that a head-to-head study

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could identify *when* each agent can provide the most effect; dexamethasone appears to work better during later stages of disease, whereas (b)(4) appears to work better at early stages.

Discussion

Dr. Beigel noted that both ACTT-1 and ACTT-2 will include proteomic analysis in order to identify biomarkers to incorporate within the ACTT study design. These analyses will be generated using Olink panels and the exact list of analytes to be tested is not yet available.

Dr. Judith Currier emphasized the importance of collecting virology data in infected patients because they will help researchers better understand COVID-19 and subsequently better inform on future therapeutics prioritization decisions within ACTIV.

Dr. Beigel noted that ACTT-2 did collect information on thrombotic events and coagulation; however, these data are not yet finalized and available for sharing.

Dr. Lundgren inquired whether ACTT-2 considered obtaining a sample of the lower respiratory tract, which is severely impacted by COVID-19 infection. Dr. Beigel noted that oropharyngeal swabs were used because they could be obtained consistently, whereas methods for lower respiratory tract sampling are not consistent.

Preclinical Agent Prioritization and Matchmaking Process

Dr. Joseph Menetski, Foundation for the NIH (FNIH)

Rationale and Inventory

Dr. Joseph Menetski described ACTIV's preclinical agent prioritization and matchmaking process. The Preclinical WG was launched to identify preclinical-stage agents that have a strong rationale for mechanism of action (MOA) against COVID-19 but require short-term preclinical development support and to facilitate that support by matchmaking applicants with sponsors. The Preclinical WG developed an inventory of all Biosafety Level 3 (BSL3) research sites and relevant animal models (mostly hamster and non-human primates [NHP]) to identify appropriate sponsors for each prioritized applicant.

Scoring Process

Each compound undergoes multiple reviews at each stage of which reviewers must either advance the agent or designate it as 'No Go'. After an agent passes through triage (i.e., survived the first review), it is reviewed by members of an agent class-specific Preclinical Subteam using Stage 1 scoring criteria, which include requirements for in vitro and in vivo data, PK/PD data from animal model testing, and a promising MOA. The agent will subsequently be reviewed according to Stage 2 scoring criteria, which include a request for data related to toxicology, clinical safety, human PK/PD, drug-drug interactions, and scalability. Stage 2 reviewers are also asked to answer four questions (listed below) in order to assess whether to proceed with matchmaking, defer the agent, or designate it as 'No Go.'

- What is the realistic timeline for these experiments (less than or more than 1 year)?
- Does this agent rise to the level of matchmaking?

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- Where are the gaps in preclinical experiments?
- Should this agent be re-evaluated later?

Matchmaking Process

If an agent is selected for matchmaking, the Preclinical WG contacts a possible sponsor within the Preclinical inventory to discuss its possible involvement in facilitating preclinical development (either preclinical studies, phase I clinical trials, or NHP studies). The WG then facilitates discussions between the sponsor site and the applicant, who will decide whether to proceed with the match or reinitiate the site matching process. Upon match agreement, the sponsor will begin the designated preclinical work. The sponsor and applicant will then update the agent's data package and submit it for re-review by the Preclinical WG.

Current Status

Thus far, the Preclinical WG has evaluated over 30 agents and recommended 21 agents for matchmaking (which are listed below according to step in the matchmaking process).

- **Six agents awaiting response from the sponsor site:** (b) (4) [redacted] (b) (4) [redacted]
- **Six agents in the site matching process:** (b) (4) [redacted] (b) (4) [redacted]
- **Five agents matched with a sponsor site:** (b) (4) [redacted] (b) (4) [redacted]
- **Four agents completed sponsored work and resubmitted the data package:** (b) (4) [redacted] (b) (4) [redacted]

Dr. Stacey Adam invited participants to share additional questions and comments with her via email.

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Appendix A: Participants List

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Samuel Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Joan Butterton, MD, *VP, Clinical Research, Infectious Diseases, Merck & Co.*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

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Carl Garner, PhD, *VP, Global Regulatory Affairs, Eli Lilly*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI*

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Elliott Levy, MD, *Senior VP Global Development, Amgen; TransCelerate Board Member*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

Daniel Rubin, PhD, *Division of Biometrics IV, CDER, FDA*

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Michelle Culp, MPH, *Office of the Director, NIH*

David Douglas, *Former Head, Global Research and Development Project Management Office, Pfizer*

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Peter Wung, MD, MHS, *Associate VP, Global OMD Lead, Immuno-Inflammation, Sanofi*

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Helen Q. Chen, PhD, *Manager, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

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Appendix B: Chat Transcript

From Eric Hughes to Everyone: 01:03 PM

Yoo-hoo 24!

From Timothy G. Buchman to Everyone: 01:03 PM

So excited to hear the ACTT-2 results...!

From Carlos Garner to Everyone: 01:06 PM

John has done a great job on this study.

From Currier, Judith, M.D. to Everyone: 01:10 PM

That is impressive enrollment.

From Timothy G. Buchman to Everyone: 01:17 PM

These bar charts are really powerful.

From Libby Higgs to Everyone: 01:18 PM

Agree, great visual.

From Timothy G. Buchman to Everyone: 01:24 PM

Was there any safety signal in those patients who got steroids AND bari?

From Peter Wung to Everyone: 01:27 PM

Was there any imbalance in the number of days of RDV used between the two arms as the patients used RDV anywhere from 5-10 days in the trial?

From Walter Koroshetz to Everyone: 01:27 PM

any changes in d-dimer, IL-6 or other markers of interest?

From Timothy G. Buchman to Everyone: 01:30 PM

Interesting that the middle two curves have shifted (while populations are not quite identical), but improving care...

From Currier, Judith, M.D. to Everyone: 01:30 PM

Care is improving over time!!

From Revell Phillips (DTRA) to Everyone: 01:30 PM

What is responsible for the difference between actt1 and act2 with RDV?

From Walter Koroshetz to Everyone: 01:30 PM

or virus is changing?

From Libby Higgs to Everyone: 01:30 PM

Yes consistent with national trends on decreasing mortality

From Timothy G. Buchman to Everyone: 01:30 PM

Secular changes in care...

From Revell Phillips (DTRA) to Everyone: 01:30 PM

Was there any change in standard of care?

From Timothy G. Buchman to Everyone: 01:31 PM

Better choices on ventilation and likely on anticoagulation.

From Libby Higgs to Everyone: 01:31 PM

Certainly more consistent use of anti-thrombotics,

From Timothy G. Buchman to Everyone: 01:33 PM

^^^^^Has certainly changed in our clinical environments.

We need to split out Mech vent alone from those who are going on to ECMO

From Neil Aggarwal to Everyone: 01:33 PM

Published ECMO outcomes have been better than expected, but agree with Tim.

From Walter Koroshetz to Everyone: 01:33 PM

So looks like ICU care hasn't made much progress vs. the virus???

From Eric Hughes to Everyone: 01:34 PM

thank you for sharing your data! great example of collaboration! 👍

From Timothy G. Buchman to Everyone: 01:34 PM

@Walter, actyually there has been enormous progress. I have accepted a short report on those improvements, will be happy to send on to you.

From Judith Hochman to Everyone: 01:38 PM

Do you have data on thrombotic events and use of anticoagulation?

From Revell Phillips (DTRA) to Everyone: 01:42 PM

can we get a copy of the slides?

From Joan Butterton to Everyone: 01:43 PM

The graphical presentations are outstanding

From Neil Aggarwal to Everyone: 01:43 PM

The whole presentation was tremendous, thank you John and team!

From Eric Hughes to Everyone: 02:00 PM

thank you john and joe!

From Revell Phillips (DTRA) to Everyone: 02:00 PM

Thank you!

From yves rosenberg, NHLBI to Everyone: 02:00 PM

Can we get a trial update in the mail?

From Eric Hughes to Everyone: 02:00 PM

👍💪

From Timothy G. Buchman to Everyone: 02:00 PM

Great talks!!!

High-Level Meeting Summary

The Preclinical Working Group (WG) discussed updates from the *In Vivo* Strategy, Data Portal Implementation, and BSL 3/4 Network Implementation Subgroups, as well as potential modifications to subgroup structure.

Action Items

- Drs. Colvis, Young, Menetski, and Alvarez will draft a proposal for subgroup restructuring to discuss at the next WG meeting

- Drs. Rappaport and Haigwood will inform Dr. Florence of the precise amounts needed for the strain validation in NHPs
- Dr. Menetski will share the preclinical therapeutic prioritization criteria with the WG after another meeting of the subgroup
- Dr. Sherri Hild will update the WG regarding the status of funding for NHP studies
- Any feedback regarding edits to summary pages on the NCATS OpenData Portal should be directed to Samantha Jonson and Dr. Liz Ottinger

Preclinical WG Subgroup Structure

As the Preclinical WG moves into the next phase of responsibilities, it will restructure subgroups to address the WG's new goals. This restructuring may include merging or sunsetting existing subgroups, forming new subgroups, adding new subgroup members from outside the current WG, or changing the meeting frequency of a given subgroup. The WG discussed two examples of possible restructuring:

- The BSL 3/4 Network Implementation Subgroup will shift its focus toward prioritization, coordination, and "match-making" for preclinical testing, as part of a broader shift from data collection to resource dissemination and management. . The WG expressed broad support for this transition and for changing the name of the BSL 3/4 Network Subgroup to the Preclinical Network Subgroup.
- The Data Portal Implementation Subgroup will decrease the frequency of its meetings from once per week to as little as once per month as their work moves into a maintenance phase.

Drs. Christine Colvis, John Young, Joseph Menetski, and Rosa Maria Alvarez will draft a proposal for subgroup restructuring to discuss at the next WG meeting.

Subgroup Updates

In Vivo Strategy Subgroup

Five parallel production runs for viral stock of the Washington strain have been completed and sequenced. In two viable production runs performed in VeroE6 lines (one additional run was not viable), the number of single nucleotide polymorphisms (SNPs) detected ranged from one to three in approximately 20-30 percent of reads. All SNPs mapped to nonstructural proteins. In the two production runs performed in Dr. Baric's VeroE6 cell lines with high ACE2 expression, no SNPs were detected, although a 56-nucleotide deletion was detected in 18% of reads from one of the runs. Yield was approximately the same across all production runs.

Without replicating the production runs, it is difficult to state definitively that the high ACE2-expressing lines are a better choice for stock production than the generic VeroE6 lines. However, Dr. Clint Florence recommended that stock production proceed in Dr. Baric's high ACE2-expressing lines given the lower SNP frequency. This recommendation is contingent upon confirmation that the shift away from VeroE6 lines will not cause unnecessary complications for the assay development team at (b) (4).

(b) (4) can perform two 20-liter production runs each month. Each run requires two weeks of production and three weeks of quality control testing, but a new run can begin immediately upon completion of each production phase; therefore, the first lot will become available in five weeks but a new lot will be completed every two weeks thereafter, provided there are no complications.

The WG expressed support for prioritizing the D614G strain (the current predominant strain circulating in humans) for the first 20-liter production run. However, Drs. Jay Rappaport and Nancy Haigwood emphasized the importance of obtaining both this strain and the Washington strain for a validation study in NHPs. Dr. Florence noted that lots from two of the five already completed production runs of the Washington strain may be distributed for this purpose; with yields of 120 ml and 500 ml, there is enough to proceed with the halted OWS vaccine studies and the strain comparison in NHPs while also retaining some stock for distribution to other groups (e.g., (b) (4)). Experimenters should be aware that the titer of these particular lots is likely too low for aerosol studies, unless conducted with IT/IN administration. Drs. Rappaport and Haigwood will inform Dr. Florence of the precise amounts needed for the strain validation in NHPs.

The NPRC group should finish master protocols for NHP experiments within the next week; management of the coordinating center is the primary remaining focus. Box will act as a repository for all current SOPs to provide version control and several SOPs are already available. Local regulatory approval and acquisition of funding are both outstanding items that are being actively addressed.

Data Portal Implementation Subgroup

The NHP detailed summary pages are now available on the NCATS OpenData Portal. The detailed summary pages for small animal models (including mouse, ferret, and hamster) are being finalized and should be published to the NCATS OpenData Portal during the first week of August. As the Subgroup moves into the maintenance phase, it will work with IT staff to create new Portal features, such as auto-alerts for people who want to be notified about new uploads. Subgroup members will also refine and add information to existing summary pages; all feedback regarding such edits should be sent to Samantha Jonson and Dr. Liz Ottinger.

Dr. Cat Lutz has updated summaries of the K18-hACE2 mouse model of severe infection following several recently submitted preprints on bioRxiv, including evidence of a dose response to SARS-CoV-2. The Subgroup will discuss the evaluation and incorporation of preprints and newly published data at its next meeting.

BSL 3/4 Network Implementation

The Subgroup is working on a preclinical agent prioritization model as well as a web-based REDCap form to solicit additional information needed from BSL 3/4 sites to understand capacity and capabilities. This group discuss preclinical therapeutic priorization as the next steps in the preclinical WG mandate. Dr. Menetski will share the proposed preclinical therapeutic prioritization criteria with the WG after another meeting of the subgroup.

Next Steps

Drs. Colvis, Young, Menetski, and Alvarez will draft a proposal for subgroup restructuring to discuss at the next WG meeting. Drs. Rappaport and Haigwood will communicate with Dr. Florence regarding how much of the Washington strain production run stock should be set aside for a strain comparison study in NHPs. Dr. Sherri Hild will update the WG regarding the status of funding for NHP studies. Any feedback regarding edits to summary pages on the NCATS OpenData Portal should be directed to Samantha Jonson and Dr. Liz Ottinger. Dr. Menetski will share the prioritization criteria for preclinical compounds upon completion.

Appendix A: Participants List

WORKING GROUP MEMBERS

Annaliesa Anderson, PhD, (not in attendance) *Vice President and CSO Bacterial Vaccines, Pfizer*

Ralph Baric, PhD, (not in attendance) *Dept. of Epidemiology and Dept. of Microbiology and Immunology, UNC Chapel Hill*

Kara Carter, PhD, *Executive Vice President Infectious Disease, Evotec*

Marc Charette, PhD, *Division of Cardiovascular Diseases NIH, NHLBI*

Tomas Cihlar, PhD, *VP, and Head of Virology, Gilead*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Damon Deming, PhD, *Virologist, Division of Antiviral Products, Office of New Drugs, FDA*

Michael Diamond, MD, PhD, (not in attendance) *Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University*

Prabhavathi Fernandes, PhD, *Retired, most recently led biotechs Cempra and DarPharma*

Josh Fessel, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Clint Florence, PhD, *Program Officer, Research Resource Section, OBRR, DMID, NIAID*

Greg Gatto, PhD, *Drug Development Regulatory Project Leader, RTI*

Jay Grobler, PhD, *Director, Infectious Disease Biology, Merck*

Nancy Haigwood, PhD, *Director and Professor, Oregon National Primate Research Center, OHSU*

Judith Hewitt, PhD, *Deputy Director, Office of Biodefense, Research Resources and Translational Research, NIAID*

Samantha Jonson, MPS, (not in attendance) *Special Assistant to the Director, NCATS*

Cat Lutz, PhD, *Senior Director, Mouse Repository & In Vivo Pharmacology, Rare and Orphan Disease Center, Jackson Laboratory*

Frank Nestle, MD, (not in attendance) *Global Head of Immunology Therapeutic Research Area and Chief Scientific Officer North America, Sanofi*

Liz Ottinger, PhD, *Project Manager, NCATS*

David Payne, PhD, DSc, (not in attendance) *Vice President & Head, Medicine Opportunities Research Unit, GSK*

Louise Pitt, PhD, *Director, Center for Aerobiological Sciences, USAMRIID*

Tony Punturieri, MD, PhD, (not in attendance) *Division of Lung Diseases NIH, NHLBI*

Srinivas Rao, MBA, PhD, *Global Head Translational In Vivo Models, Sanofi*

Jay Rappaport, PhD, *Director and Chief Academic Officer, Tulane Primate Center*

John Young, PhD, *Global Head Infectious Diseases and Vice President, Roche*

INVITED PARTICIPANTS

Sheri Hild, PhD, *Program Director for the National Primate Research Centers (NPRCs) at Office of Research Infrastructure Programs, NIH*
Isis Kanevsky, PhD, *Unit Director, Pfizer*
Peter Adams, PhD, *Health Scientist, Project Officer, BARDA*
Ken Duncan, PhD, *Gates Foundation*

FNIH STAFF
Stacey Adam, PhD, *Director, CancerResearch Partnerships, FNIH*
Joseph P. Menetski, PhD, *Associate VP, Research Partnerships, FNIH*

Rosa Maria Alvarez, PhD, *Senior Consultant*, *Monitor, Deloitte*
Benjamin Stratton, PhD, *Manager, Deloitte*

Caroline Sferrazza, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Judy Hewitt to Everyone: 10:14 AM

I would prefer to call the network Preclinical, rather than BSL3/4

From Christine Colvis to Everyone: 10:14 AM

Very good point

From Kara Carter to Everyone: 10:14 AM

completely agree.

From hildsa to Everyone: 10:49 AM

Were links to these pages distributed?

From Christine Colvis to Everyone: 10:50 AM

There are only mock ups now

From Nancy Haigwood to Everyone: 10:51 AM

Hard to hear; could others please mute?

From Jay Rappaport to Everyone: 10:53 AM

Cat, maybe you could try reduce volume on speaker as it may be echoing

From cat lutz to Everyone: 10:57 AM

sorry had to move from my office--someone is mowing lawn next door.

From Kara Carter to Everyone: 10:58 AM

sorry, I need to leave

From Srinivas Rao to Everyone: 10:58 AM

bye all

From Judy Hewitt to Everyone: 11:00 AM

my sound just quit working, so signing off

From Christine Colvis to Everyone: 11:00 AM

I need to hop off

leading antoher meeting

High-Level Meeting Summary

The Vaccines Working Group (WG) convened to receive updates and commendations from Dr. Francis Collins and discuss its current and future priorities.

ACTIV Leadership's Acknowledgement of Efforts

Dr. Collins thanked Vaccines WG members and the teams at FNIH and Deloitte for their dedication to addressing the needs of the vaccine research field during this unprecedented moment. He praised the WG for its harmonized master protocol for vaccine efficacy trials, which informed the design of vaccine clinical trials initiated this week (i.e., Moderna and NIH) and those to be initiated in upcoming months (e.g., AstraZeneca/Oxford, Novavax, and J&J). Dr. Collins also emphasized the importance of both manuscripts developed by the Vaccines WG. He noted that the WG's publication on human challenge studies was a thoughtful analysis of both ethical and operational challenges that highlighted how these studies would not accelerate vaccine development more than an efficacy trial; although NIH is still considering performing these studies in tandem with ongoing trials, it will make significant efforts to ensure safety. Further, he praised the manuscript on vaccine-associated enhanced disease, which will inform approaches to this challenge during vaccine development.

Dr. Collins noted that at this time, the Vaccines WG will transition from weekly to as-needed meetings. If the WG's capabilities and efforts are required to address an additional challenge in the future, the Co-chairs will schedule a meeting to reconvene the group.

Dr. Doug Lowy thanked Dr. Collins for his continued support, responsiveness, and leadership across all Vaccines WG efforts. Dr. Michael Santos recognized the launch of Moderna/NIH and Pfizer/BioNTech trials and congratulated Vaccines WG members on their efforts.

Current and Future Priorities

The Vaccines WG was launched in mid-April and quickly expanded to include three Sub-Groups, each with its own specific objective. The WG's Co-Chairs, Drs. Doug Lowy and Kathrin Jansen, have presented biweekly updates to ACTIV leadership on the WG's and its subgroups' progress for the last three months. In accordance with the original ACTIV timeline, WGs were charged with reevaluating their priorities during July. ACTIV leadership asked the Vaccines WG to discuss and establish its current and future priorities in order to ensure the WG efficiently uses its members' time and maintains its capabilities.

This reevaluation led to the decision to hold future Vaccines WG meetings on an as-needed instead of weekly basis, with Drs. Lowy and Jansen reporting progress to ACTIV leadership when applicable. The WG's two ongoing priorities are (1) publishing its vaccine-associated enhanced disease manuscript and associated summary for a broader audience and (2) considering the implications of the first successful vaccine against COVID-19 on other ongoing vaccine development programs.

Participants proposed the following objectives for the upcoming months, summarized below:

- Assay harmonization and development of complementary assays to identify correlates of protection across vaccines and enable bridging studies
- Considerations related to vaccinating children and pregnant women
- Enrollment of underserved sub-populations within vaccine efficacy trials and coordination of community engagement efforts across ACTIV, NIH, and CoVPN

Participants discussed several of these priorities in greater detail.

Assays. Dr. Tal Zaks inquired whether other partnerships or institutions are prioritizing assay harmonization and use across vaccines to support the identification of correlates of protection, and whether discussing those topics within the WG would be valuable or duplicative of other efforts. Dr. Larry Corey noted that there is activity within Operation Warp Speed and that the correlates analysis plan is being led by Peter Gilbert working with the sponsors' biostatisticians. However, he suggested that awareness into work on these topics should still be a priority within the Vaccines WG, and will be for the Vaccines Clinical Trials Sub-Group. Dr. Ann Arvin also noted that there is more thought required to enable bridging studies, including across vaccines, and suggested that it's worth considering additional, more sophisticated, assays that could be used. Dr. Lowy agreed with the value of considering these topics.

Children and pregnant women. Dr. Arvin raised the topic of planning to evaluate vaccines for pediatric populations, with the question about the right time to consider that issue. Dr. Lowy agreed with the importance of that issue, and suggested that additionally the topic of vaccine evaluation in pregnant women continues to be important. Dr. Kathy Neuzil agreed that as work on those topics moved forward she thought it would be valuable to be able to consult the WG. Dr. Paul Gillard also suggested the importance of studying pediatric administration.

Community Engagement. Dr. Nelson Michael emailed ahead of the meeting to suggest that the topic of community engagement to enable representative enrollment of the clinical trials be discussed within ACTIV. Dr. Corey noted that ACTIV and NIH are pursuing approaches to improve community engagement in vaccine efficacy trials and suggested that this could be a topic for discussion in August.

Vaccine-Associated Enhanced Disease (VAED). Dr. Barton Haynes pointed out that the VAED article from the WG found that it was unliked that VAED would be distinguishable from natural disease, and asked if there is already thinking about assays within the clinical trials to attempt to distinguish this, if it occurred, beyond the typical evaluations of vaccine safety.

Dr. Corey emphasized that the manuscript has been influential in the way that people are thinking about and addressing this topic. He noted that the DSMB formed a group of clinicians who will monitor and characterize disease. Dr. Corey suggested that if there is a perspective about an assay that could be considered before a phenotype is observed, that is something that could be advised on.

Dr. Santos summarized that there is clear interest from the group in the topics of correlates of protection, which will be discussed within the Vaccines Clinical Trials Sub-Group. An important question is whether that conversation will focus on the statistical and portfolio aspects, or also engage on more detailed discussion of assays. Dr. Corey suggested that the Vaccines WG invite the investigators performing assays during clinical trials to present during a future WG meeting; participants agreed. Dr. Arvin suggested that discussions of different topics benefit from an understanding of each other, and can be part of one group.

The Vaccines Working Group itself will meet in the future when there is need, but for now another meeting is not scheduled. Drs. Jansen and Lowy will remain in contact with ACTIV leadership and will convene the Working Group when either they or leadership identify a topic for the group to discuss. The Vaccines Clinical Trials Sub-Group plans to meet every other week going forward; Dr. Santos invited Vaccines WG members who do currently participate in the Vaccines Clinical Trials Sub-Group to contact him if they would like to be added.

Appendix A: Participants List

WORKING GROUP MEMBERS

Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI)*
Paula Annunziato, MD, *Vice President, Vaccine Clinical Development, Merck*
Ann Arvin, MD, *Professor of Pediatrics and Microbiology & Immunology, Stanford University*
Susan Buchbinder, MD, *Director of Bridge HIV, San Francisco Department of Public Health, and Professor, UCSF*
Larry Corey, MD, *Professor and Principal Investigator, University of Washington and HIV Vaccine Trials Network, and Past President and Director, Fred Hutchinson Cancer Research Center*
Gregory Glen, MD, *President, Research and Development, Novavax*
Barton Haynes, MD, *Director, Human Vaccine Institute, Duke University School of Medicine*
Peter Hotez, MD, PhD, *Dean for the National School of Tropical Medicine, Baylor College of Medicine, and Director, Texas Children's Center for Vaccine Development*
Peter Marks, MD, PhD, *Director, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA)*
Michael Santos, PhD, *Associate Vice President, Science, FNIH*
Jim Tartaglia, PhD, *Vice President, Research and Development, Sanofi Pasteur*
Brett Tolman, MA, *Strategy Manager, Deloitte*
Tal Zaks, MD, PhD, *Chief Medical Officer, Moderna Therapeutics*

INVITED PARTICIPANTS

Francis Collins, MD, PhD, *Director, NIH*
Michelle Culp, BSN, MPH, *Senior Advisor, Office of Science Policy, NIH*
Paul Gillard, MD, *Senior Director, Clinical Development, GlaxoSmithKline (GSK)*
Holli Hamilton, MD, MPH, *Senior Medical Officer, BARDA*
Kathy Neuzil, MD, MPH, FIDSA, *Director, Center for Vaccine Development and Global Health, University of Maryland School of Medicine*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*
Stephanie Schrag, DPh, *Epidemiology Team Lead, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, CDC*
Natalie Thornburg, PhD, *Lead Microbiologist, Respiratory Viruses Branch, CDC*

FNIH STAFF
Stacey Adam, PhD, *Director, Foundation for the NIH (FNIH)*
Stephanie James, PhD, *Senior VP of Science, FNIH*
Karen Tountas, PhD, *Scientific Program Manager, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Jonathan Wachtel, MBA, *Manager, Deloitte*

Bethany Stokes, MS*, Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard updates from both its Master Protocol and Agent Prioritization Subgroups (MPSG and APSG, respectively), and planned for its meeting next week.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4).

ACTIV-1: Immunomodulators (Inpatient Phase III)

The ACTIV-1 team received its second round of pre-IND feedback from FDA on August 10 and is currently addressing comments. The team has also finalized its Informed Consent Form and will submit the form to FDA along with its master protocol. It continues working with NCATS' Trial Innovation Network (TIN), which will oversee the trial's operational planning and implementation. The NCATS/BARDA team has selected a CRO partner to support the trial's implementation; BARDA is finalizing contracts. The ACTIV-1 team will submit its IND application soon and expects to launch its trial by late August or early September.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

The ACTIV-2 master protocol launched on August 3. As of August 12, five sites are open with additional sites being onboarded daily. The ACTIV-2 team expects to enroll its first patient soon and has been working with Operation Warp Speed (OWS) leadership to acquire additional rapid testing machines and kits for participating sites. The team has also been evaluating vendors for providing home health services and will soon select one and issue a contract. The team is also preparing to launch its public relations (PR) campaign to raise awareness and expedite patient recruitment. The team will hold a kickoff meeting with AstraZeneca next week to begin incorporating its agent into the master protocol as well.

Drs. Stacey Adam and Judith Currier agreed to arrange a presentation of ACTIV-2's PR campaign during a future TX-Clinical WG meeting.

Discussion

Dr. Adam introduced TX-Clinical WG members to the slide templates that will be used to report to OWS on the status of both ACTIV-2/-3, including tested products and activated sites, enrolled patients, and geographical overlap between activated sites and COVID-19 cases. Dr. Carl Garner asked whether these slide templates will reflect the present status of ACTIV-2/-3 (e.g., agents *being* tested) or show projected information (e.g., agents *expected* to be tested). Dr. Adam will follow up on this question.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

The ACTIV-3 master protocol launched and was officially announced on August 4. As of August 12, six sites were open and had (b)(4). The ACTIV-3 team has been working with OWS leadership to secure adequate supply of (b)(4) and to ensure continuous activation of additional sites; the 20-patient DSMB Safety Review for (b)(4) agent is scheduled for end of August, and the team expects to complete Stage 1 enrollment in September. The team also continues to work with GSK Vir and Brii Bio to incorporate their agents into the master protocol and will hold a kickoff meeting with AstraZeneca next week to start incorporating its agent.

Discussion

Participants confirmed that neither ACTIV-2 nor ACTIV-3 enforce minimum enrollment criteria by patients' demographic groups (e.g., neither requires that a specified proportion of patients enrolled be female or of a particular ethnic minority group), but they emphasized the need to closely monitor demographic trends in each trial's patient pool to ensure that each trial adequately represents patient populations most affected by COVID-19.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4's pre-hospitalized and hospitalized protocols have received DSMB approval, and both protocol teams are prepared to submit final responses to minor comments from a central IRB. Both protocols are expected to launch early during the week of August 24. The outpatient convalescent clinical (post-hospitalization) trial will soon be submitted for DSMB review. OWS has informed the ACTIV-4 team that it will likely receive its supply of (b)(4) [redacted] in September.

Agent Prioritization Subgroup Updates

The APSG continues to prioritize agents in parallel across four classes: neutralizing antibodies (Abs) and associated compound, antivirals, immune modulators, and symptomatic/supportive therapies. Beyond the summaries below, further details on all agents being evaluated can be found in the appendix slides of the deck presented during this meeting.

Neutralizing Antibodies and Associated Compounds

The ACTIV-2/-3 Agent Selection Committee (ASC) has so far evaluated 10 neutralizing Abs, of which five have been endorsed by the TOC to advance to the trial teams (approvals contingent on promising Phase I data). The ASC has also begun to review new agent types that mimic the activity of neutralizing Abs (e.g., designed ankyrin repeat proteins and polyclonal antibodies) from companies such as Molecular Partners. The ASC also reviewed (b)(5) [redacted] The ASC recommended t(b)(5) [redacted]

Antivirals

The Antiviral Subteam has conducted a second-round review of camostat mesylate and (b)(4) [redacted]. For camostat mesylate (oral formulation), the team has engaged with (b)(4) [redacted] to gauge its interest in participating in ACTIV-2; the company expressed interest, but because it is located (b)(6) [redacted], the Subteam needs to assess any potential manufacturing complications. For (b)(4) [redacted], the Subteam is requesting additional data from the company for further evaluation of the PK/PD.

Immune Modulators

The Immune Modulators Subteam has conducted a second-round review of (b) (4) [redacted] and montelukast, and identified a path forward for each candidate. (b) (4) [redacted]. In collaboration with the Preclinical WG, the Subteam initiated Wave 3 Agent Prioritization, and is now evaluating 18 compounds in Wave 3's first round.

Symptomatic/Supportive Therapies

In collaboration with the Preclinical WG, the Symptomatic/Supportive Subteam has completed Wave 2 assessment of 14 symptomatic/supportive therapies. The Agent Prioritization Review Committee (APRC) has reviewed the Subteam recommendations and has approved TXA127 to be tested (recommend for the Big Effect Trial) and has rerouted (b) (4) [redacted] for Wave 3 evaluation by the Immune Modulators Subteam.

Options for Next Week's Meeting

The TX-Clinical WG meeting scheduled for August 20 at 1:00pm ET conflicts with the next nAb clinical summit, which is scheduled to occur that day between 12:30 and 4:05pm ET, and which several WG members want to attend. The summit agenda is organized around a set of topics (list below) for which white papers will be written. Lead authors for each topic and panels of topic experts will lead discussions of their corresponding sessions during the summit:

- Safety – Antibody-Dependent Enhancement
- Safety – Epitope Binding and Viral Resistance
- Efficacy – Effector Function and Antibody Optimization
- Efficacy – Learnings from Other Fields
- Assay Development – Assay Standardization

The summit will be viewable through the NIH Videocast platform. Dr. Adam will forward the link to that platform to all TX-Clinical WG members.

TX-Clinical WG members agreed to try to reschedule its meeting next week and to arrange its rescheduled time around the availability of representatives from the National Heart, Lung, and Blood Institute's (NHLBI) CONNECTS (Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies) effort, who will present its efforts to the WG.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, NHLBI*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Joan Butterton, MD, *VP, Clinical Research, Infectious Diseases, Merck & Co.*

Timothy H. Burgess, MD, MPH, *Captain, Navy*

Sylva Collins, PhD, *Director of the Office of Biostatistics, FDA*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Carl Garner, PhD, *VP, Global Regulatory Affairs, Eli Lilly*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute (NHLBI)*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, NIAID, NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

Daniel Rubin, PhD, *Division of Biometrics IV, CDER, FDA*

INVITED PARTICIPANTS

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, NCATS, NIH*

Michelle Culp, MPH, *Office of the Director, NIH*

David Hone, PhD, *Chief Scientist, Vaccine and Therapeutic Division, Joint Science and Technology Office (JSTO)*

Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*

Hilary D. Marston, MD, MPH, *Medical Officer/Policy Advisor, NIAID, NIH*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Revell Phillips, PhD, *Science and Technology Manager, Defense Threat Reduction Agency*

Christine Sizemore, PhD, *Director, Division of International Relations, Fogarty International Center, NIH*

John Young, PhD, *Global Head Infectious Diseases and Early Development, Roche*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*
Olivia Elsaid, *Strategy Consultant, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Timothy G. Buchman: 17:45

Very nice format. What will constitute a "hot spot?"

Timothy G. Buchman: 19:24

Ignore my question. Found it at the bottom of the frame in small print.

Ruxandra Draghia-Akli: 19:52

Congratulation for the opening of the sites and early enrollment!!!

Eric Hughes: 20:20

great progress!

Timothy G. Buchman: 21:10

So happy to see these enrollments starting! What a great validation of the interactions among the teams and companies and OWS!

Carlos Garner: 22:43

I really like these reports

Eric Hughes: 33:29

Stacey- are more monoclonals coming in for evaluation? -Eric

Timothy G. Buchman: 33:44

The timeline slide is really helpful. Can OWS add the candidate vaccines timelines to that medical countermeasures?

Timothy G. Buchman: 35:09

By "timeline slide", I mean the Neutralizing product antibodies "Estimated Product Readiness" slide

Timothy G. Buchman: 41:28

Thank you Stacey and team for all you do!!!

Action Items

- Ms. Resnansky will review the eConsent playbook and provide feedback.
- Ms. Desrosiers will ask a colleague in Merck's consent group to review the eConsent playbook and provide feedback.
- Dr. Tountas will send the eConsent playbook to Judy Currier and Peter Kim at ACTG for their review and feedback.

High-Level Meeting Summary

The Clinical Trial Capacity Working Group (CTC WG), co-chaired by Elizabeth Desrosiers and Michael Kurilla, convened to receive a debrief of the Executive Committee meeting on July 14, 2020 and to discuss playbook development and revisions to survey questions.

Below is a summary of the key discussion themes.

Playbooks

The WG Co-Chairs explained that the playbook concept has been well received throughout ACTIV. The status of playbook development is as follows:

- The Mobile Nursing playbook should be complete by COB July 14. The final version will be saved in the WG's Basecamp folder. The ACTIV-2 operations team is already using this playbook.
- The eCOA/BYOD Hybrid playbook is in progress and will be submitted for review by July 17.
- The eConsent playbook is complete. Many commercial eConsent platforms already exist, and their use requires specific information directly from the vendor. Therefore, this playbook focuses on considerations for study teams when selecting a platform, which may be dictated by the patient population and geographic location of the trials.
    - Ms. Resnansky will review this playbook and provide feedback.
    - Ms. Desrosiers will ask a colleague in Merck's consent group to review the playbook and provide feedback.
    - Dr. Tountas will send the eConsent playbook to Judy Currier and Peter Kim at ACTG for their review and feedback.
- The Remote Monitoring playbook is in progress and will be submitted for review soon.
- The Site Training and Tools playbook is in progress and will be submitted for review by July 17. Forthcoming information from Merck's meeting planning group and the NIH Clinical Center will supplement the existing content.

WG members are encouraged to review and submit feedback on all of the playbooks once complete.

Anyone who meets the broad definition of being involved in ACTIV will have access to the playbooks. Dr. Tountas is exploring whether the playbooks can be linked to and downloaded from the dashboard.

The WG Co-Chairs and FNIH staff will pursue options for maintaining the currency of the playbooks over time.

Survey

To maintain the usefulness of the dashboard, the survey data must be periodically refreshed. The Survey sub-WG recently met to review the network and site surveys to identify questions that should be added, deleted, or revised before asking networks and sites to update their responses—perhaps during the fall after the larger COVID-related studies have launched. The sub-WG's list of recommended changes focused on the *site* survey, because no sub-WG member expressed concern about the network survey. Some of the revisions included (1) as a follow-on to question 18, asking sites that report being involved in a COVID trial to identify whether it is an ACTIV trial and under which network and (2) revising question 22 to ask whether the site has a location where symptomatic COVID patients can receive infusion in an outpatient settings.

WG members expressed concern about the amount of time required for sites to update their responses. They offered the following suggestions to reduce respondent burden:

- Delete questions that also appear on the network survey. For example, if the network demonstrates experience to conduct master, adaptive, and platform protocols, then ACTIV should rely on the quality control processes of the network to ensure that the sites also possess that same experience.
- Retain questions that are truly useful in the site selection process and that only the site can answer, such as experience with eConsent and telehealth and access to PPE.
- Retain questions about the site's capacity to conduct inpatient and outpatient trials, which will change over time.

Dr. Kurilla stated that work to revise the surveys will continue and will be informed by this feedback.

Closing Comments

A WG member stressed the importance of continuing this WG's work after July—not only to maintain the currency of the dashboard and playbooks, but also to support the field as it seeks to conduct trials in settings that are not part of existing networks, such as nursing homes, long-term care facilities, and meat packing plants.

Appendix A: Participants List

WORKING GROUP MEMBERS

Myron Cohen, MD, *Associate Vice Chancellor for Global Health and Medical Affairs, Director, Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill*

Victoria Davey, PhD, MPH, *U.S. Department of Veterans Affairs*

Elizabeth Desrosiers (Co-Chair), MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

James Dickens, *Program Manager, National Center for Advancing Translational Sciences*

David Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI)*

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Laura Resnansky, *Vice President, Global Head of Clinical Operations – Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Genentech*

Christine Sizemore

Michael Vincent, MD, PhD, *Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

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Penny Heaton, MD, *Chief Executive Officer, Bill & Melinda Gates Medical Research Institute*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis*

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Stephanie James, PhD, *Senior VP of Science*
Benjamin Stratton, *Senior Consultant, Deloitte*
Karen H. Tountas, PhD, *Scientific Program Manager, Science*
Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard updates from both its Master Protocol and Agent Prioritization Subgroups (MPSG and APSG, respectively), and reviewed the status of NIAID's Big Effect Trial.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4), and Dr. Stacey Adam noted that she is working to arrange a monthly meeting involving representatives of all four protocols to help align their efforts where relevant.

ACTIV-1: Immunomodulators (Inpatient Phase III)

The ACTIV-1 team has addressed FDA's comments and submitted responses and an amended protocol to FDA on August 3. It continues to work with NCATS' Trial Innovation Network (TIN), which will oversee operational planning and trial implementation. TIN has received "expressed interest" from 49 of its sites to participate in ACTIV-1. The NCATS Team is also working with BARDA on CRO selection and contracting, which will be executed by August 15. NIAID is sponsoring the Data Safety Monitoring Board (DSMB) for ACTIV-1, which held its first meeting on August 5. The ACTIV-1 team will amend the protocol based on DSMB comments made during that meeting.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

Three ACTIV-2 sites are ready to enroll their first patients. Unexpected issues in procuring suitable methylhistamine urine tubes have delayed first patient enrollment; this problem is expected to be solved imminently. A recent Facebook Live chat hosted by Drs. Francis Collins and Anthony Fauci garnered significant attention, helping to promote the ACTIV-2 trial and spur recruitment. The ACTIV-2 team will continue to activate additional sites in preparation for expanding patient enrollment. The team is working to expand home health options for the trial and will soon execute a contract with a vendor to provide services for in-home infusions. The team is also still working with Merck representatives to incorporate their agents into the master protocol. The Trial Oversight Committee (TOC) has endorsed AstraZeneca's agent to enter ACTIV-2, and the team will soon hold a kickoff meeting to begin incorporating that agent into the protocol.

Discussion

Participants noted that the OWS and ACTIV teams are now developing a strategy to allocate reagents and other testing resources appropriately across clinical and research sites, while test machines and kits are in short supply. Dr. Judith Currier will also contact Dr. John Mellors to further discuss this resource allocation strategy and how it will affect research sites; Dr. Carl Garner noted that he may be able to arrange supplies of reagents or other testing supplies for research labs. Dr. Garner also agreed to connect Dr. Currier with (b)(4) [redacted] Operations Lead for its ongoing ambulatory trial to share insights on how to speed ambulatory patient enrollment.

Participants favored Dr. Revell Phillips' proposal that ACTIV sites administer influenza testing as fall approaches and this becomes a confounding factor for the COVID testing.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

The ACTIV-3 master protocol launched and was officially announced on August 4. As of August 5, one site was open and had enrolled its first patient; additional sites will be onboarded daily. The team has been working with OWS leadership to secure adequate supply of (b) (4), and additional shipments of the drug are expected to arrive during the next week. The team is also still working with GSK-Vir to incorporate its agents into the master protocol and will continue working with both GSK-Vir and AstraZeneca (whose agent was endorsed by the TOC for ACTIV-3) to finalize their agent-specific appendices and to plan for trial operations and logistics. The team will report back to the TX-Clinical WG on the status of the trial as additional sites (including in Europe) are activated and more patients are enrolled.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4's hospitalized trial launch has been slightly delayed by operational hurdles. The three ACTIV-4 trials are expected to launch on the following dates: (1) hospitalized, August 13; (2) pre-hospitalized, August 17; (3) post-hospitalized, August 30. The ACTIV-4 team continues to seek drugs for its post-hospitalized cohort. Dr. Adam noted that NHLBI's Dr. Amy Patterson will be invited to a future TX-Clinical WG meeting to present on NHLBI's newly launched CONNECTS (Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies) effort.

Agent Prioritization Subgroup Updates

The APSG continues to prioritize agents in parallel across four agent classes: neutralizing Abs, antivirals, immune modulators, and symptomatic/supportive therapies.

Neutralizing Antibodies

The ACTIV-2/-3 Agent Selection Committee (ASC) has so far evaluated eight neutralizing Abs, of which four have been endorsed by the TOC to advance to the trial teams (approvals contingent on promising Phase I data). OWS leadership has requested that (b) (4) be removed from ACTIV trials because (b) (5); appropriate next steps are being discussed.

The ASC will soon review several new agent types, including DARPins (designed ankyrin repeat proteins) and polyclonal antibodies.

Antivirals

With the Preclinical WG and OWS, the Antivirals Subteam has completed Wave 2 assessment of 34 antivirals, and the Agent Prioritization Review Committee (APRC) has reviewed the Subteam recommendations. The Subteam has also obtained and positively reviewed additional data for camostat mesylate, and it will meet with company representatives for this agent to discuss trial logistics. The Subteam is also collecting further data on (b) (4) for review.

Immune Modulators

In collaboration with the Preclinical WG, the Immune Modulators Subteam completed Wave 2 assessment of 28 immune modulators; the APRC has reviewed the Subteam recommendations.

The Subteam is following up with investigators to obtain additional data on (b) (4) [redacted] and montelukast for further evaluation.

Symptomatic/Supportive Therapies

In collaboration with the Preclinical WG, the Symptomatic/Supportive Subteam has completed Wave 2 assessment of 14 symptomatic/supportive therapies. The APRC has reviewed Subteam recommendations, and the Subteam is soliciting from investigators additional data on TXA127 and avdoralimab for further evaluation.

NIAID's Big Effect Trial

Following up on a previous TX-Clinical WG discussion about the NIAID Big Effect Trial (BET), Dr. Beigel noted that BET's Phase II study infrastructure could help ACTIV to generate further data on agents of interest that already have sufficient preclinical data, but for which the ACTIV team desires further *clinical* evidence before advancing to a larger Phase III inpatient trial in either ACTIV-1, -3, or -4. As a proof-of-concept study, BET aims to identify promising treatments that can then enter a more definitive trial, which—in addition to ACTIV trials—could also include ACTT or industry-sponsored trials (especially for smaller companies needing support for early trials).

The BET master protocol has been drafted and adapted for two agents: BET-A will test the anti-IL-23 agent risankizumab, and BET-B will test the anti-GM-CSF agent lenzilumab. The protocol will be submitted to FDA the week of August 10, with trial launch anticipated for August 31.

Dr. John Beigel also noted that the NIAID Division of Microbiology and Infectious Diseases' (DMID's) Infectious Diseases Clinical Research Consortium trial network frequently conducts Phase I studies and could be leveraged to help agent sponsors generate Phase I data for the nAbs or other agents needed to support entry into ACTIV Phase II trials.

Discussion

Dr. Beigel confirmed that BET trials will collect both clinical and lab-based data that will supply NIAID with objective measures to inform go/no-go decisions for specific compounds.

Appendix A: Participants List

WORKING GROUP MEMBERS

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Michelle Culp, MPH, *Office of the Director, NIH*

Ellen Gadbois, PhD, *Office of Science Policy, Office of the Director, NIH*

David Hone, PhD, *Chief Scientist, Vaccine and Therapeutic Division, Joint Science and Technology Office (JSTO)*
Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*
Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*
Hilary D. Marston, MD, MPH, *Medical Officer/Policy Advisor, NIAID, NIH*
Ashley Parker, PhD, *Health Science Policy Analyst, NIH*
Revell Phillips, PhD, *Science and Technology Manager, Defense Threat Reduction Agency*
Ronald Reisler, MD, *Senior Clinical Advisor at David Defense Group, JPEO-CBRND-JPM CBRN Medical*
Allan Shipp, MHA, *Senior Clinical Research Policy Analyst, Office of Science Policy, NIH*
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Olivia Elsaid, *Strategy Consultant, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Revell Phillips: 25:11

We also had questions about adding in flu testing

Eric Hughes (EU): 26:53

flu testing critical. both at enrollment and during analysis.

Chen, Helen Q.: 44:20

(b) (5)

Revell Phillips: 55:23

What is the plan for moving a drug that has success in the BET trial forward quickly.

Sam Bozzette: 01:01:26

does big effect mean "statistically significant" with a big effect size? what about a modest effect size with a trend toward significance?

High-Level Meeting Summary

The Preclinical Working Group (WG) discussed the status of (b)(4) viral stock production; the 'match-making' process for nonhuman primate (NHP), small animal, and *in vitro* studies; and updates from the *In Vivo* Strategy, Data Portal Implementation, and Preclinical Network Implementation Subgroups.

Viral Stock Production

(b)(4) has harvested the first 1L stock of virus from the new round of production runs. The stock was grown in Dr. Ralph Baric's high ACE2-expressing VeroE6 cell line and harvested after appearance of cytopathic effect (CPE) in 50% of the monolayer. Certified titer analysis showed an improvement from the previous round of production runs, with a titer of 1.5×10^6 PFU/ml. Sequencing analysis of this stock will be available by the week of August 24.

Three more 1L production runs are currently underway at (b)(4) using different multiplicities of infection (MOIs) in the standard (b)(4) cell line. These cultures were infected on Monday August 17 and will be harvested according to the same CPE observation guideline.

(b)(4) also plans to seed a HYPER*Flask* with the New York isolate (D614G) strain in VeroE6 cells later this week. Dr. Jay Rappaport noted that the initial 1ml aliquot of D614G virus received from (b)(4) contained approximately 50% mutation in the dibasic furin cleavage site. Dr. Clint Florence will communicate with (b)(4) regarding these mutations.

Two backup stock production efforts are underway at Battelle; titers are being measured for the first harvested stock and a molecular clone is also being investigated with aid from BARDA.

'Match-making' Process for NHP and Small Animal/*In Vitro* Studies

WG members reviewed the 'match-making' process and its role within that process, noting that they should all communicate a consistent message when discussing this process with colleagues that are interested in proposing studies.

The Preclinical WG does not have any role in approving NHP, small animal, or *in vitro* studies for COVID-19, but rather provides guidance regarding prioritization of these studies. This guidance will be provided to an NIH COVID Expert Panel for NHP studies and to NIAID or other sponsors for small animal and *in vitro* studies. The Expert Panel for NHP studies is currently being assembled and will include members of this WG as well as NIH representatives and other experts with knowledge of Operation Warp Speed or related endeavors. The Expert Panel will also receive study requests from external sources (e.g., COVID R&D). A portal will be designed, with help from NCATS, to compile all information that the Expert Panel will review during its meetings. Dr. Sheri Hild will send suggestions from the Expert Panel and the NIH Office of Research Infrastructure Programs (ORIP) to the NPRC's Operations Committee and research advisory committees (RACs). NPRCs will handle directly any non-COVID NHP study requests.

Dr. Rappaport will amend a draft letter, aimed at to those interested in working with NPRCs, to clarify that approval of NHP studies comes from the NIH COVID Expert Panel and ORIP.

Subgroup Updates

In Vivo Strategy Subgroup

The Best Practices for COVID-19 Research in Small Animal Models Subteam met to discuss topics to include in the field guide, and members volunteered to begin drafting ideas for each topic. Drafts will be uploaded to BaseCamp and compiled by Dr. Rosa Maria Alvarez before the Subteam's next meeting.

The WG discussed creating guidance on virus source and strain to ensure consistent viral protocols. Given that many labs work with small animals, not all of them will be able to use (b)(4) virus stocks. Still, the field guide will designate the Washington strain as the benchmark strain for studies in small animals. Studies performed with the Washington strain produced from non-(b)(4) stocks, but within a defined sequence variability, should be considered comparable to each other and to studies performed using (b)(4) stocks. Studies performed with any other virus strain should be considered informative regarding questions about the impact of different single nucleotide polymorphisms (SNPs) but not for ongoing drug development. Best practices for reporting SNPs (as compared to the benchmark) in publications will be included in the field guide.

Data Portal Implementation Subgroup

During its last meeting, the Subgroup discussed the goals, use cases, and operational logistics for a study-level animal model analytical data platform. The Subgroup seeks to leverage the existing infrastructure being developed by Tulane (for an unrelated project) to create a data hub for all NPRCs. Following its proof-of-concept validation, this same data hub design could be adapted and implemented for small animal models. The Subgroup will meet with the Tulane team on Thursday, August 20 to discuss this platform; representatives from NIAID will attend and will share lessons learned from similar platforms built for anthrax and ebola studies.

Preclinical Network Implementation Subgroup

The Subgroup conducted its first agent adjudication this week. It sent letters to submitters of clinical compounds that have been deferred for preclinical testing, requesting that they sign Confidential Data Agreements (CDAs). Once CDAs are executed, the Subgroup will meet with the agent submitters to determine if they can produce the necessary data on their own, and if submitters lack the resources to generate the required data, then they will be matched with a facility that has the appropriate capacity and capabilities to produce those data.

The prioritization process for preclinical compounds, which mirrors the Therapeutics-Clinical WG's agent prioritization model, requires adjustment before preclinical compound prioritization can proceed apace. Specific aspects of the process to be addressed by the Subgroup include the following:

- Separating compounds by class (e.g., antivirals, immunomodulators) before evaluation

- Distinguishing preclinical compounds in early stages of investigation from those that already have substantial supporting data, such that promising compounds with a strong rationale do not receive bad scores by default because they lack data

The Subgroup is nearing completion on its BSL3 survey, which will be sent to previously identified BSL3 sites by August 29.

Next Steps

Dr. Florence will discuss the mutations observed in Dr. Rappaport's D614G virus aliquot with (b)(4). Dr. Rappaport will amend a draft letter to those interested in working with NPRCs to clarify that the NIH COVID Expert Panel and ORIP will be charged with approving NHP studies. Dr. Alvarez will compile all submitted field guide draft materials before the Best Practices for COVID-19 Research in Small Animal Models Subteam's next meeting.

Appendix A: Participants List

WORKING GROUP MEMBERS

Peter Adams, PhD, (not in attendance) *Health Scientist, Project Officer, BARDA*

Ralph Baric, PhD, *Dept. of Epidemiology and Dept. of Microbiology and Immunology, UNC Chapel Hill*

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Tomas Cihlar, PhD, *VP, and Head of Virology, Gilead*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Damon Deming, PhD, (not in attendance) *Virologist, Division of Antiviral Products, Office of New Drugs, FDA*

Michael Diamond, MD, PhD, (not in attendance) *Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University*

Ken Duncan, PhD, *Gates Foundation*

Prabhavathi Fernandes, PhD, *Retired, most recently led biotechs Cempra and DarPharma*

Josh Fessel, MD, PhD, (not in attendance) *Division of Lung Diseases NIH, NHLBI*

Clint Florence, PhD, *Program Officer, Research Resource Section, OBRR, DMID, NIAID*

Greg Gatto, PhD, *Drug Development Regulatory Project Leader, RTI*

Jay Grobler, PhD, (not in attendance) *Director, Infectious Disease Biology, Merck*

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Cat Lutz, PhD, *Senior Director, Mouse Repository & In Vivo Pharmacology, Rare and Orphan Disease Center, Jackson Laboratory*

Stephen Mason, PhD, *Associate Research Fellow, Pfizer*

Frank Nestle, MD, (not in attendance) *Global Head of Immunology Therapeutic Research Area and Chief Scientific Officer North America, Sanofi*

Liz Ottinger, PhD, *Project Manager, NCATS*

David Payne, PhD, DSc, (not in attendance) *Vice President & Head, Medicine Opportunities Research Unit, GSK*

Louise Pitt, PhD, *Director, Center for Aerobiological Sciences, USAMRIID*

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Caroline Sferrazza, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Participants did not use the Zoom chat function during this meeting.

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) received updates from the July 15 Executive Committee meeting, as well as from both its Master Protocol and Agent Prioritization Subgroups (MPSG and APSG, respectively), and viewed a presentation from the Vaccines WG.

Executive Committee Meeting Update

Trial Recruitment Strategy

On July 4, NIH leadership, NIAID COVID-19 Prevention Trials Network (CoVPN) representatives, and ACTIV Vaccines WG members, Drs. Larry Corey and Nelson Michael, met to discuss current strategies to enroll patients from high-risk subpopulations (i.e., African Americans, American Indians/Alaska Natives, Latinx, older adults, and pregnant women). Drs. Corey and Michael then initiated a community engagement campaign to help enroll these subpopulations for upcoming vaccine trials and this week launched a website that details the strategies employed in this campaign.

Representatives from NIH, ACTIV, and CoVPN also met with Moderna leadership to discuss collaborative opportunities to enroll diverse groups into an upcoming Phase III vaccine trial. On July 13, NIH launched the ACTIV Community Engagement WG, led by NHLBI Director and ACTIV Executive Committee member Dr. Gary Gibbons, and NIMHD Director Dr. Eliseo Perez-Stable; this WG will (1) develop an action plan to quickly and effectively engage high-risk populations for all upcoming ACTIV clinical trials and (2) connect NIH community partners within diverse communities to the CoVPN. Dr. Stacey Adam noted that the TX-Clinical WG will soon develop a website similar to that developed by Drs. Corey and Michael, detailing strategies for enrolling high-risk patients in therapeutics clinical trials.

Discussion

Dr. Sarah Read asked how the newly formed Community Engagement WG will interface with the TX-Clinical WG. Mr. David Wholley noted that the Community Engagement WG is currently focused on enrolling patients in vaccine trials scheduled to begin imminently; however, focus will soon expand to include therapeutics trials. Dr. Read stressed that community engagement will be critical to ACTIV-2's outpatient study and will require robust collaboration between the Community Engagement WG and the TX-Clinical WG. The Trial Oversight Committee's (TOC's) Dr. Janet Woodcock aims to develop an overarching community engagement board and has directly engaged with the Indian Health Service in these efforts.

Mr. Wholley will share with Dr. Francis Collins and ACTIV leadership the TX-Clinical WG's interest in more robustly connecting with the Community Engagement WG. Dr. Adam will share with Mr. Wholley the email addresses of Drs. Read, Judith Currier, David Wall; Mr. Wholley will then connect these three individuals with the Community Engagement WG.

Master Protocol Subgroup Updates

Dr. Adam briefly reviewed the status of the MPSG's master protocols now under development:

- **ACTIV-1:** (phase III; immunomodulators; inpatients; Pre-IND submitted; late-August launch)
    - Agents: (b)(4)
    - Sponsor: TBD + NCATS Trial Innovation Network (TIN) + CRO
- **ACTIV-2:** (phase II/III; neutralizing monoclonal antibodies [nMABs]/ oral antivirals; outpatients; IND submitted; late-July launch)
    - Agents: (b)(4) nMAB and (b)(4)
    - Sponsor: NIAID AIDS Clinical Trials Group (ACTG) + CRO
- **ACTIV-3:** (phase III; nMABs; inpatients; Pre-IND comments returned from FDA; July launch)
    - Agents: (b)(4) nMAB and (b)(4) nMAB
    - Sponsor: NIAID INSIGHT + NHLBI PETAL + NHLBI CTSN + VA + CRO
- **ACTIV-4:** (phase III; anticoagulants; pre-hospitalized/hospitalized/post-hospitalized; protocol submitted to DSMB; July launch)
    - Agents: TBD
    - Sponsor: NHLBI-NINDS Network of Networks

ACTIV-1: Immunomodulators (Inpatient Phase III)

Dr. Samuel Bozzette updated that the ACTIV-1 team is working with (b)(4) to engage one of (b)(4) s existing CROs to manage ACTIV-1 studies. Responses from these CROs are expected next week and the ACTIV-1 team will select a CRO the following week. Enrollment is expected to begin during late August to allow all contracts and subcontracts with the (b)(4) CRO to be finalized.

The ACTIV-1 team has assigned NCATS staff to support these clinical trials and has developed the ACTIV-1 consent form; it is finalizing the protocol and discussing operational considerations.

Among the 49 Clinical and Translational Science Awards (CTSA) program hubs, nine affiliate sites and one nonaffiliate site have expressed interest in participating in ACTIV-1. Each site received a survey from the ACTIV-1 team and responses are expected next week.

Discussion

Dr. Currier asked whether sites that have been identified for both ACTIV-1 and ACTIV-3 trials will conduct multiple trials per site. Dr. Bozzette noted that no co-enrollment will occur and that individual sites will choose whether to conduct multiple, simultaneous trials (although each site will likely participate in only one protocol at a time).

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

Dr. Judy Currier updated that the ACTIV-2 team is awaiting a ‘safe to proceed’ response from FDA and approval from its IRB; the team expects to launch its trial during late-July, and has initiated community engagement public relations campaigns and seeks to collaborate with the ACTIV Community Engagement WG. It has endorsed the entry of (b)(4) into its protocol and will meet with representatives from (b)(4) on July 17 to discuss incorporating this agent into the protocol appendix.

The ACTIV-2 team received input from other TX-Clinical WG teams regarding how to implement home-health capabilities within the outpatient trials as well as to track the epidemic to prioritize site activation, especially within Florida and the southwestern United States. It also received the updated IB and anticipates that FDA will not mandate 4-hour observation post-infusion because data do not appear to support it.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

The ACTIV-3 team has submitted its IND, and Dr. Elizabeth Higgs will share with the TX-Clinical WG the finalized submission. The ACTIV-3 team has also discussed potential concerns regarding increased post-infusion observation times and has decided to include 2 hours of post-infusion observation, with the option for longer monitoring when needed. Sites expressed concern that intensive monitoring of adverse events will impact enrollment. The ACTIV-3 team will have its DSMB review the protocol once 20 patients are enrolled to ensure that the protocol addresses necessary safety and speed challenges.

Operation Warp Speed (OWS) would like ACTIV-3 to proceed as quickly as possible, and the ACTIV-3 team is discussing how to balance speed and safety. It is also now selecting national clinical trial sites to be “Vanguard” clinical sites for the trial and expects to later select additional “Vanguard” sites in Europe. The DSMB will assess the status of ACTIV-3 upon enrollment of 20 patients; if the protocol is approved, the ACTIV-3 team will expand to 40 sites and subsequently 100 total sites during Stage 2 of the protocol.

Discussion

Dr. Adam confirmed that ACTIV-3 includes an appendix allowing certain sponsors to submit agents for phase I study (i.e., institutions that lack the resources or mechanisms to support a phase I trial); such sponsors must express interest in a phase I trial within their application to the Agent Select Committee, which will evaluate which stage of testing to proceed with.

Dr. Lisa LaVange noted that at the recent FDA Real-World Evidence meeting, researchers from Oxford considered whether ACTIV’s approach to clinical trial facilitation may be too cautious; however, FDA has been closely involved with ACTIV and has assured the group that protocols are not too restrictive (i.e., data collection can be reduced if warranted). Dr. Peter Stein noted that most of the agents to be assessed in ACTIV trials have not been tested elsewhere and that therefore, FDA requires that baseline safety data be generated; however, FDA also understands that the pandemic also requires flexibility. Dr. Stein invited TX-Clinical WG members to contact him with any remaining concerns regarding the flexibility of FDA’s requirements and procedures.

Dr. Garner noted that ACTIV-3 requires consistent collection of safety data across all clinical trial sites, which is critical because ACTIV-3 focuses on hospitalized patients. Participants agreed that the ACTIV-3 team should review safety and monitoring requirements for agents nominated for its trials before approving those agents for testing. The TX-Clinical WG will continue this discussion in a future meeting.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4 includes three clinical trial platforms: (1) pre-hospitalized, (2) in-hospital, and (3) post-hospitalization.

Pre-Hospitalized

The ACTIV-4 team has submitted its pre-hospital trial protocol to the Steering Committee and expects feedback later today; the team will submit the protocol to its DSMB on July 17 and the DSMB will discuss the protocol during a July 27 meeting.

In-Hospital

The DSMB approved the in-hospital trial protocol with minor comments, which are being incorporated by the ACTIV-4 team. When this process is finished, the team will submit the protocol for IRB approval. This protocol will not require an IND and thus the ACTIV-4 team anticipates rapid initiation of trials at multiple sites shortly after IRB approval.

Post-Hospitalization

The ACTIV-4 team has developed a template for its post-hospitalization protocol—an adaptive, two-arm study of oral anti-coagulants versus placebo. Investigators involved in ACTIV-4 have proposed three possible study arms for this protocol: (1) any anti-coagulant prescribed at patient discharge, compared to placebo, (2) specific anti-coagulant prescribed to patients who lack insurance, compared to placebo, and (3) specific industry-supported anti-coagulant agent, compared to placebo. Option (3) is currently activated within the pre-hospital trial, using the Pfizer anti-coagulant Apixaban.

The ACTIV-4 team has estimated a (b) (4), (b) (5) [redacted]. Following discussions with ACTIV-1 investigators, investigators involved in ACTIV-4 expressed (b) (4), (b) (5) [redacted] for some of the master protocols. Dr. Andrei Kindzelski noted that cost differences will create competition among ACTIV-4's trial networks, particularly CTSA sites. He also noted that the ACTIV-4 team is pursuing partnerships with industry to expand the label of anti-coagulants and stressed the need to further discuss differences in cost.

Discussion

Dr. Kindzelski noted that ACTIV-4 is very interested in co-enrollment opportunities; Dr. Adam will schedule a meeting with representatives from all TX-Clinical WG protocol teams to discuss cost and co-enrollment considerations for ACTIV-4.

Dr. Timothy Buchman asked whether co-enrollment may confuse outcomes if the trial includes a single standard of care reference arm. Dr. Kindzelski noted that anti-coagulation has become standard of care in hospitals and will be assessed differently than in other ACTIV protocols. All ACTIV-4 platforms are adaptive, and thus the team can add or subtract study arms in real time to account for co-enrollment opportunities. Dr. Currier noted that some ACTIV-2 trial sites do not have capacity for infusions but do have capacity for oral therapies; these sites could enroll patients for ACTIV-4. Dr. Currier will contact Dr. Kindzelski to discuss this opportunity further.

Agent Prioritization Subgroup Updates

Dr. Adam briefly summarized APSG updates, shown below.

Neutralizing Antibodies

The Neutralizing Antibodies Subteam evaluated seven neutralizing antibodies. The TOC endorsed four of these agents to advance to the trial teams.

Antivirals

The Antivirals Subteam completed its Wave 2 assessment of 23 agents and the TOC endorsed one agent ((b)(4) [redacted]) for testing. The Subteam has requested additional information on four of the agents already evaluated.

Immunomodulators

The Immunomodulators Subteam has completed its Wave 2 assessment of 12 agents and will evaluate another 12 agents this week.

Symptomatic/Supportive Therapies

The Symptomatic/Supportive Therapies Subteam is collecting candidate submissions and will soon begin to evaluate agents.

Vaccines WG Presentation

The ACTIV Vaccines WG has three main priorities, summarized below:

- **Priority 1:** Support harmonized efficacy trials to accelerate traditional vaccine approval.
- **Priority 2:** Identify biomarkers and other evidence to accelerate vaccine approval or authorization.
- **Priority 3:** Address safety questions regarding COVID-19 vaccine development, particularly those associated with vaccine-associated immune enhancement

The Vaccines WG's approach to efficacy trials does not include master protocol platform trials but does include a common implementation framework that is supported by the CoVPN and supplemented by CROs on specific features (e.g., centralized labs, single DSMBs). The Vaccines WG aims to facilitate harmonization across all vaccine trials to ensure that clinical trial results from both government and nongovernment developers are comparable. Multiple vaccine efficacy trials (e.g., Moderna, Pfizer) are expected to launch during July, with more trial launches expected during upcoming months.

Harmonization of vaccine trial protocols will allow for identification of cross-trial insights as well as correlates of protection to help accelerate vaccine development. The primary endpoint for the Vaccine WG's harmonized protocol will be virologically confirmed symptomatic disease, and its secondary endpoint will be infection and moderate-to-severe disease. Enrollees will include adults of all ages (assuming safety is confirmed in older adults) and a subset of seropositive individuals; the Vaccines WG understands the need to enroll diverse participants representative of the United States population. Success criteria for each trial will be a resulting vaccine efficacy of above 50 percent with a lower bound of the 95 percent confidence interval below 30 percent. The Vaccine WG anticipates that each trial will enroll 30,000 participants with 2:1 randomization and that its primary analysis results will be achieved within 6 months.

Dr. Michael Santos presented discussion topics from recent Vaccines WG meetings:

- Specific definitions for endpoints, especially endpoints for severe disease
- Power required to assess efficacy against severe disease
- Evaluation of safety and efficacy in pregnant individuals
- Analysis of correlates of protection
- Implications of the first vaccine success for other ongoing trials

Discussion

Dr. Mellors asked what type of placebo would be used in the event that a successful vaccine candidate is licensed. Dr. Santos noted that FDA will likely issue Emergency Use Authorization and that timeline from primary analysis to licensure will likely be shortened. He also noted that the Vaccines WG has discussed ethical concerns around continuation of placebo trials after a successful vaccine candidate is identified and that a successful vaccine will likely be prioritized for deployment in specific at-risk populations.

Dr. Koroshetz asked whether vaccine efficacy trials will target healthcare workers for enrollment. Dr. Santos noted that vaccine trials will not focus on healthcare workers but will focus on enrolling patients from subpopulations with disproportionately adverse outcomes. Dr. Adam noted that other prevention and vaccine trials, such as the Patient-Centered Outcomes Research Institute's Healthcare Worker Exposure Response and Outcomes trial, are focused on enrolling healthcare workers.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, NHLBI*

Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Carl Garner, *PhD, Vice President, Global Regulatory Affairs, Eli Lilly and Company*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute (NHLBI)*

Walter Koroshetz, MD, *Director, National Institute of Neurological Diseases and Stroke (NINDS)*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Sandeep Menon, PhD, *Senior VP and Head of Early Clinical Development, Pfizer*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, NIAID, NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

Daniel Rubin, PhD, *Division of Biometrics IV, CDER, FDA*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

INVITED PARTICIPANTS

John Beigel, MD, *Associate Director for Clinical Research, Division of Microbiology & Infectious Diseases, NIAID*

Timothy H. Burgess, MD, MPH, *Captain, Navy*

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, NCATS, NIH*

Michelle Culp, MPH, *Office of the Director, NIH*

Ellen Gadbois, PhD, *Office of Science Policy, Office of the Director, NIH*

Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*

Elliott Levy, MD, *SVP, Global Development, Amgen*

Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*

Hilary Marston, MD, *Medical Officer/Policy Advisor, NIAID, NIH*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*
Revell Phillips, PhD, *Science and Technology Manager, Defense Threat Reduction Agency*
Michael Santos, PhD, *Associate Vice President, Science, FNIH*
Brett Tolman, MA, *Strategy Manager, Deloitte*

STAFF
Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*
Karen Tountas, PhD, *Scientific Program Manager, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Timothy Buchman to Everyone: 01:06 PM

Excellent. This inclusive approach embodies responsible leadership of the highest order.

From Hilary Marston to Everyone: 01:10 PM

Yes, CoVPN has a specific community engagement effort for Native Americans

From Walter Koroshetz to Everyone: 01:14 PM

Any discussion come up about competing protocols with different per patient costs that might influence which trials a group decides to pick up?

From Stacey Adam to Everyone: 01:23 PM

There has been some coordination between ACTIV-1.2. and 3

We had not had a chance to loop on ACTIV-4

From Sam Bozzette to Everyone: 01:39 PM

Can you review option 2 again?

From Timothy Buchman to Everyone: 01:45 PM

Does co-enrollment lead to confusion in outcomes if there is a SOC reference arm in 1-2?

From Timothy Buchman to Everyone: 01:56 PM

This gets precisely to my concern, thanks for articulating it so clearly.

From Libby Higgs to Everyone: 01:57 PM

The practical issue is that no vaccine can be manufactured to cover the globe.

From Walter Koroshetz to Everyone: 01:58 PM

As I understand it: Outcome in ACTIV 4 is a thrombotic event. That rate could be reduced by effective anti-viral, or hypothetically by an immunmodulator. Question for other trials is whether choice of anticoagulation would affect their outcome. Not much of a problem if both beneficial or one neutral. Trouble comes if concern that treatments have opposing effects?

targeting health care workers?

Will vaccine trials make special efforts to enroll health care workers? Any other populations targeted?

From John Mellors to Everyone: 02:00 PM

Thanks Mike!

From Neil Aggarwal to Everyone: 02:00 PM

Thank you

From Jacqueline Kirchner to Everyone: 02:00 PM

thank you, Mike! nice to hear your voice.

From Timothy Buchman to Everyone: 02:00 PM

Thanks to all!!!

High-Level Meeting Summary

The Clinical Trial Capacity Working Group (CTC WG), co-chaired by Elizabeth Desrosiers and Michael Kurilla, convened its final meeting to receive commendations from Dr. Francis Collins and to hear a last set of updates on the CTC WG's activities, the Dashboard GeoTracking Tool, and the Innovation Playbooks.

The Dashboard GeoTracking Tool will soon be migrated to a National Center for Advancing Translational Sciences (NCATS) server and possibly migrated to a National Institute of Allergy and Infectious Diseases (NIAID) server in the future.

Three Innovation Playbooks have been finalized and are available for use. The final two Playbooks will soon be finalized and made available. The Playbooks will be hosted on the NCATS server and Dr. Mike Kurilla will share a link when it becomes available. For the next month, Playbooks will be accessible on Basecamp.

Below is a summary of the key discussion themes.

ACTIV Leadership's Acknowledgement of Efforts

Dr. Francis Collins thanked the CTC WG members and teams at FNIH and Deloitte for their efforts to facilitate the objectives and activities of ACTIV. Dr. Collins emphasized that the WG far surpassed its original scope. Its ability to collect all relevant information on more than 50 clinical trial networks and 700 sites, with unprecedented speed and efficiency, directly facilitated ACTIV's progress and the upcoming initiation of many ACTIV trials. ACTIV-2, ACTIV-3, and ACTIV-4 are expected to begin this week, whereas ACTIV-1 will begin in August. Dr. Collins noted that the information collected and the capabilities of the GeoTracking Tool directly informed matchmaking between ACTIV protocols and clinical trial sites in areas with high case rates. Further, he emphasized that the legacy of the CTC WG will live on within the Innovation Playbooks, which will be informative for researchers facilitating clinical trials in any scientific domain.

Mr. David Wholley and Ms. Betsy Desrosiers echoed Dr. Collins' acknowledgements of the CTC WG and Sub-WG members, as well as the teams at FNIH and Deloitte.

Dr. Michael Kurilla thanked ACTIV leadership for providing the support needed to facilitate the CTC WG's objectives. He also thanked Dr. Janet Woodcock, who served on the CTC WG before moving to Operation Warp Speed, for her early leadership in guiding the WG to focus on clinical trial networks and sites that were 'shovel-ready,' or had the capability to be quickly and efficiently leveraged for clinical trial initiation. He thanked CTC WG members for rapidly reviewing survey responses to ensure trials and sites were efficiently matched.

CTC Sub-WG Updates

Ms. Desrosiers presented the final deliverables for each CTC Sub-WG, summarized below:

- **Survey Development Sub-WG:** Developed, administered, and collected data from three capacity surveys targeting networks and clinical sites, CROs, and SMOs.
- **Clinical Trial Network Inventory Sub-WG:** Created an inventory of "shovel-ready" and other "specialty" networks (mostly NIH-based) to be surveyed for relevant capabilities and capacities.
- **Innovation Sub-WG:** Created an inventory of innovations and solutions to guide discussions within ACTIV clinical trial protocol and operation teams regarding efficiency considerations.

Dashboard GeoTracking Tool Updates

Dr. Kurilla and Ms. Desrosiers thanked Tanvir Ahmed, Kevin Footer, Ethan Jones, and Alyssa Long for their support in creating the Dashboard GeoTracking Tool. They noted the team mitigated many challenges in developing and providing access to the tool.

The GeoTracking Tool will soon be migrated to a National Center for Advancing Translational Sciences (NCATS) server and possibly migrated to a National Institute of Allergy and Infectious Diseases (NIAID) server in the future. Hosting the tool at NIAID would allow Kevin Footer to continue providing maintenance; Mike Tartakovsky, the Chief Information Officer at NIAID, also offered to maintain the tool. Thus far, the Dashboard Team has finalized the licenses required to facilitate the transfer to NCATS and to share the tool broadly with the scientific community.

Dr. Kurilla noted that NCATS will develop a follow-up survey to assess post-trial needs of clinical sites and facilitators involved in ACTIV clinical trials, which will inform an update to the capacity criteria within the GeoTracking Tool.

Innovation Playbooks Updates

Ms. Desrosiers presented updates on the five Innovation Playbooks, summarized below:

- **Mobile Nursing:** This Playbook has been finalized and is available for use. Ms. Desrosiers noted that the Playbook includes sections on home-health services as requested by the ACTIV-2 protocol team, which has incorporated home nursing components into upcoming trials.
- **eConsent:** This Playbook has been finalized and is available for use.
- **Site Training/Tools:** This Playbook has been finalized and is available for use.
- **Remote Source Data Verification (Remote SDV):** This Playbook will soon be finalized and made available. It includes information on how to ensure data integrity through remote measures.

- **Electronic Clinical Outcome Assessments (eCOA):** This Playbook will soon be finalized and made available. It is currently under review.

The Innovation Playbooks will be hosted on the NCATS server and Dr. Mike Kurilla will share a link when it becomes available. The CTC WG and NCATS will develop a capability to allow those requesting access to the GeoTracking Tool to receive access to the Innovation Playbooks simultaneously. During the interim, the Playbooks are available on Basecamp. Participants who do not have access to the CTC WG's Basecamp site should contact Dr. Tountas for access.

Ms. Desrosiers thanked WG members for reviewing the Playbooks and invited all participants to share the GeoTracking Tool and Innovation Playbooks with their respective organizations and colleagues.